Synthetic and Physical-Organic Approach to Functionalizations of Adamantane via Free Radical Routes(Dissertation_全文)

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Preface

In the present thesis are collected the studies carried out under the direction of Professor Iwao Tabushi (then assistant professor, Kyoto University and now professor, Department of Pharmaceutical Sciences, Kyushu University), Professor Zen-ichi Yoshida, and Professor (now emeritus) Ryohei Oda at Kyoto University during 1969-1974. The work was intended to shed light on the synthetic aspects of the adamantane chemistry.

I wish to express my grateful gratitude to Professor Zen-ichi Yoshida and Professor emeritus Ryohei Oda for their kind guidances, valuable discussions, precious comments and critisisms, and to Professor Iwao Tabushi who introduced me into the present subject and guided me throughout the work. Thanks are due to Dr. K.Fujita, Mr. K Hata, and especially to Mr. T.Okada for their technical suggestions at the beginning of the work and to Messrs. S.Kojo, N.Takahashi, M. Ozawa, and A.Togashi for their active collaborations. I am also indebted to several other people. Occasional discussions with Dr. H. Ogoshi, Dr. S.Yoneda, Dr. Y.Tamaru, and my colleagues (Messrs. H.Yamada, K.Yamamura, F.Imashiro, Y.Kuroda, and T.Nakajima) are gratefully acknowledged.

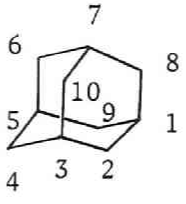
Finally, I should like to record my deep thanks to Rizo and Misae Aoyama, my parents, Toshihiro Aoyama, my brother and also to Miss Mitsuko Katayama, my fiancee, for their constant and affectionate encouragements rendered throughout the work.

Feb. 1974, Yasuhiro Aoyama

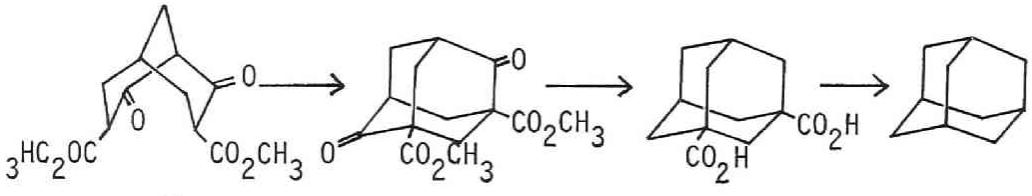
Contents

General Introduction

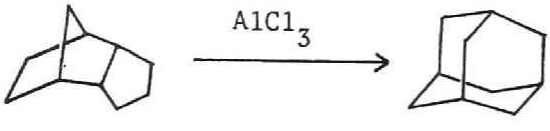
In 1933, Landa[1] isolated from petroleum a $C_{10}H_{16}$ hydrocarbon of the diamond lattice and gave a name "adamantane" from the Greek for diamond. It is the hydrocarbon, tricyclo[3.3.1.$1^{3,7}$]decane. Attempts



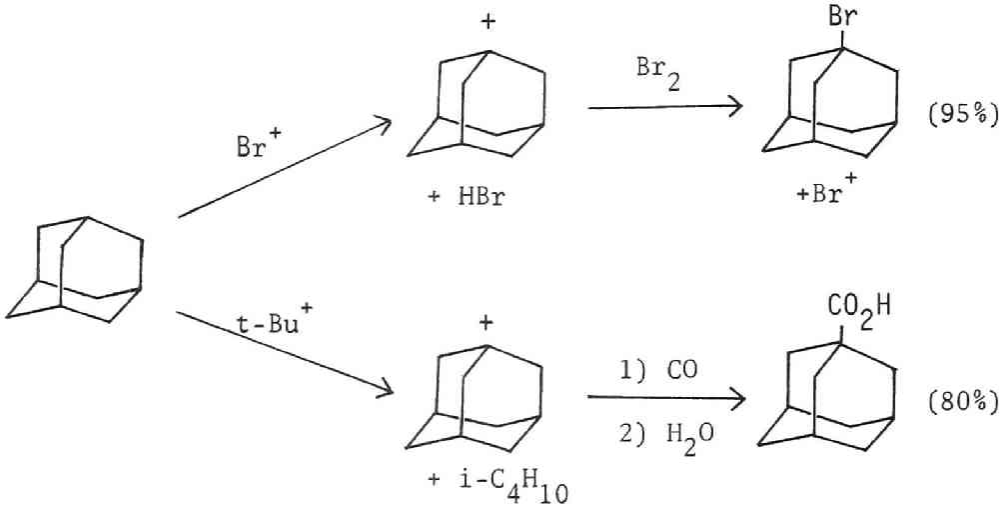
to synthesize this compound were made but with negative results until Prelog[2], in 1941, succeeded in a multistep synthesis based on the following cyclization of a bicyclo[3.3.1]nonane derivative. In 1957



Schleyer[3] discovered a convenient one step synthesis of adamantane, which has been a major contribution to the remarkable developments achieved thereafter in the chemistry of adamantane.[4]



The unique structure of adamantane, composed of three fused chair cyclohexane rings, is reflected in its "ideal" chemical properties. Adamantane but not an usual aliphatic substrate undergoes several electrophilic substitutions such as bromination[5] and carboxylation[6] with surprising efficiencies. A significant body of evidences, however,



suggests that adamantane possesses no "abnormally high reactivity. The facile electrophilic substitutions of adamantane should, then, be due to the rigid cage structure which prevents the bridgehead cation generated (and the product therefrom) to undergo further complex reactions such as intramolecular hydride shift, elimination giving an olefin, and so on. The simplified reaction paterns in adamantane thus eliminate complications which usually arise in a reaction of a flexible substrate. An importance in the synthetic chemistry of adamantane lies in this very point.

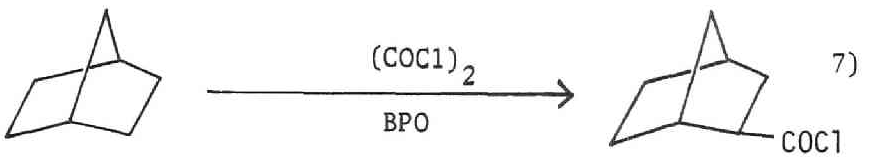
Because of the conformational fixation of adamantane, theoretical interpretations (e.g., in terms of electronic and steric effects) of reactions occurring in adamantane are the more straightforward. An interest would then be how the informations obtained from mechanistic and/or theoretical studies could be applied to successful synthetic reactions, especially regioselective functionalization of adamantane.

Strong antivirus activities shown by some derivatives of adamantane further stimulate the synthetic adamantane chemistry.

Practically countless adamantane derivatives have been prepared from theoretical, pharmaceutical, industrial, and other interests, as were substituted benzenes in the early benzene chemistry. It would be no exaggeration to say that by virtue of its ideal properties such as high symmetry and rigid but strain free structure, adamantane offers a route to new systematic aliphatic chemistry.

The present thesis deals mainly with some synthetic aspects of the adamantane chemistry, focusing upon bifunctionalization of adamantane (part 1, chapter 1-5). Various types of reactions, i.e., ionic, free radical, and carbene reactions were employed for the purpose. In principle a bifunctional adamantane may be obtained by a second substitution on a monosubstituted adamantane. In the case of adamantane having an electronegative substituent a serious electronic deactivation is usualy observed toward a second introduction of a substituent via an ionic process and vigorous conditions are required,

under which the substituent already present may undergo undesired side reactions. In these circumstances a free radical substitution is adopted as an alternative approach. Despite a wide spread concept of "low selectivity" of a radical reaction, recent investigators have found that proper choice of reagents and conditions results in a highly selective nonionic (mostly radical) reaction. Some examples are shown. Potentiality of radical reactions for synthetic purposes



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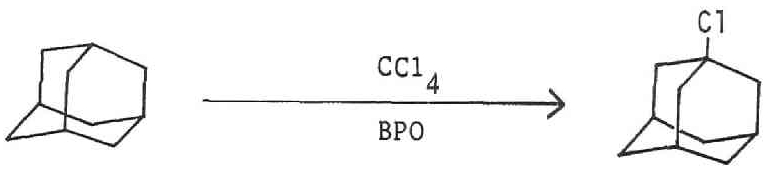

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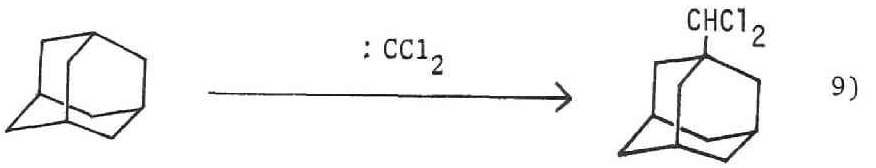

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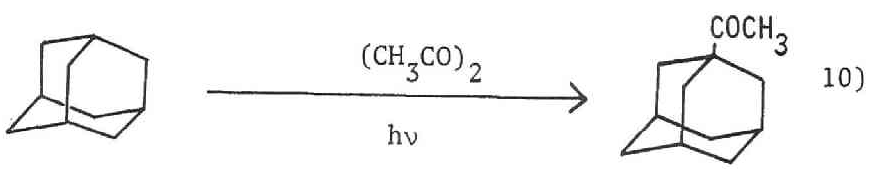

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should not be overlooked. For a future success in selective (or specific) bifunctionalization of adamantane some mechanistic studies on the aliphatic free radical reactions have also been made and are presented in the second part of this thesis. A detailed discussion is made in chapter 6 regarding the radical structure and its stability, one of the most fundamental problems of the free radical chemistry. A new idea is proposed about the rehybridization in radical formation. Nonplanarity of some strained secondary radicals is also discussed along the line. In the final chapter a detailed investigation is presented on the substituent effects on the radical halogenation of 1-substituted adamantanes. Correlation of the reactivities with the polar and steric parameters of the substituents may be one of the most important results. From these studies it has become possible to make theoretical predictions on the ease, orientation, stereochemistry, and so on of a synthetic reaction of adamantane.

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Part 1

Preparations of Adamantane Derivatives

Chapter 1

Preparations of Some 1,2- and 1,4-Disubstituted Adamantanes

1.1 Summary

From readily available 1-carboxyadamantan-2-one (1), nine 1,2-disubstituted adamantanes (2-10) were prepared. Photoacetylation of 2-acetoxyadamantane resulted in the exclusive formation of 1-acetyl-4-acetoxyadamantane (13), from which seven 1,4-disubstituted adamantanes (14-20) were derived. In some cases, novel dibromocarbene bromination was applied to the oxyesters (3 and 15). By the proto-adamantane route was prepared 1-ethyl-2-bromoadamantane (23). Autoxidation of 1-fluoroadamantane gave the 4- and 2-ketones (26 and 27) besides the bridgehead alcohol (25).

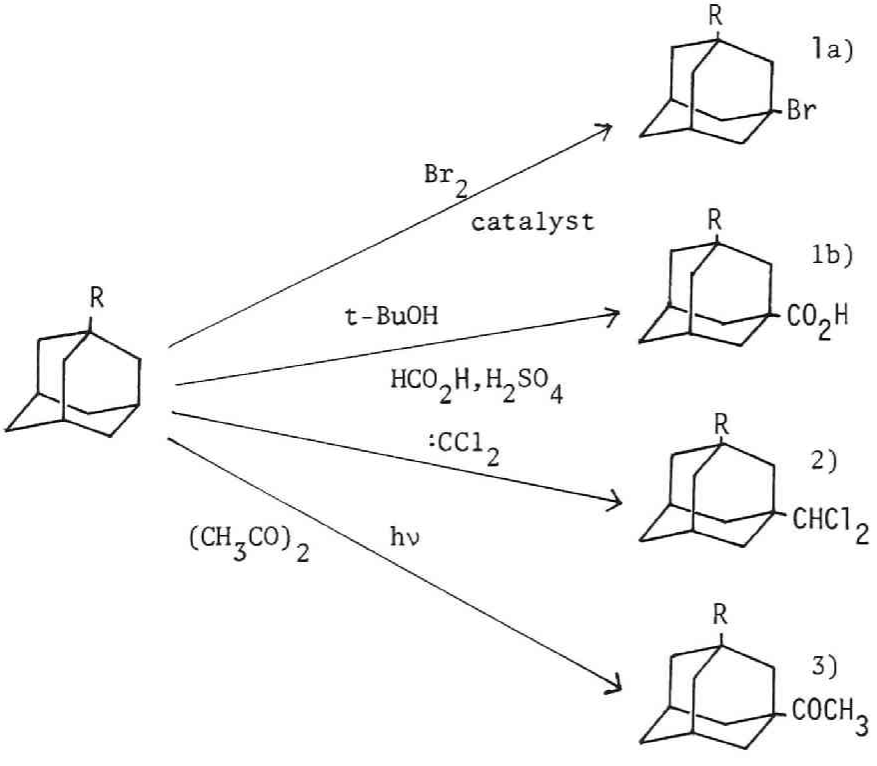
α Methine proton chemical shifts of some 1,2- and 1,4-disubstituted adamantanes are discussed from the viewpoint of additivity relationship based on the chemical shifts of monosubstituted adamantanes.

1.2 Introduction

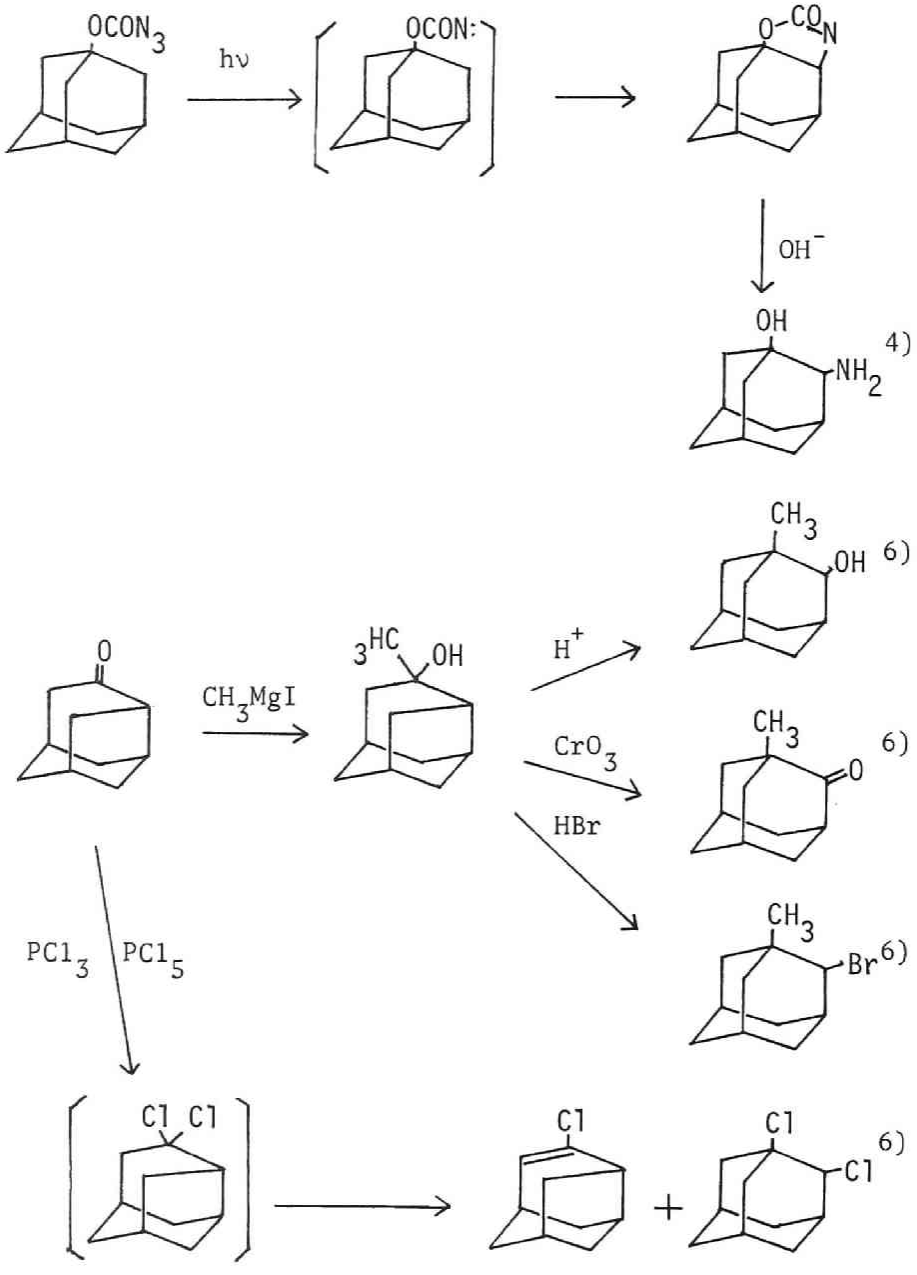
Because of its moderate rigidity and unique geometry, the chemistry of adamantanes has received much interest in recent years both from theoretical and synthetic viewpoints. High

symmetry of adamantane allows only two monosubstituted derivatives to exist. The situation is more complicated for disubstituted adamantanes ($C_{10}H_{14}XY$). When X≠Y, 13 isomers (seven chiral and six achiral) are possible. This number is reduced to nine (six achiral and three chiral) when X=Y. Regioselective difunctionalization of adamantane may be one of the most exciting synthetic challenge for adamantane chemists.

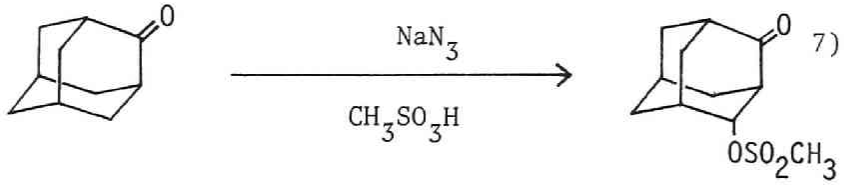
A 1,3-disubstituted adamantane may be prepared easily via direct bridgehead substitutions such as ionic substitutions,[1] dichlorocarbene insertion,[2] and photoacetylation.[3]

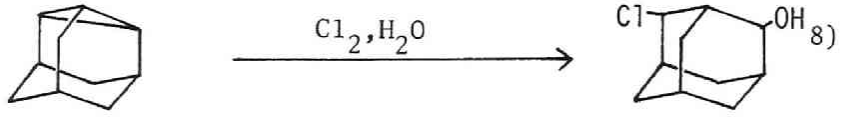


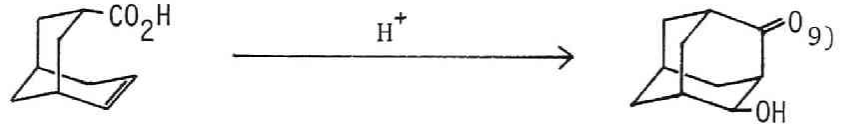
Some elegant procedures for the preparations of 1,2-disubstituted adamantanes such as intramolecular processes[4,5] and the proto-adamantane route[6] have been established. A number of 2,4-

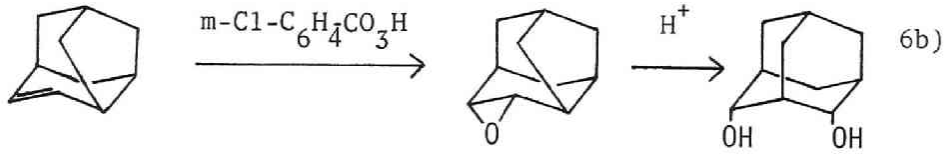


disubstituted adamantanes have also been prepared by the direct substitution of adamantanone,[7] addition reactions to 2,4-dehydroadamantane,[8] the so-called π route ring closure of bicyclo[3.3.1]non-3-ene systems,[9,10] or the protoadamantane route.[6,11] On the other hand, only limited works have been reported on the 1,4-

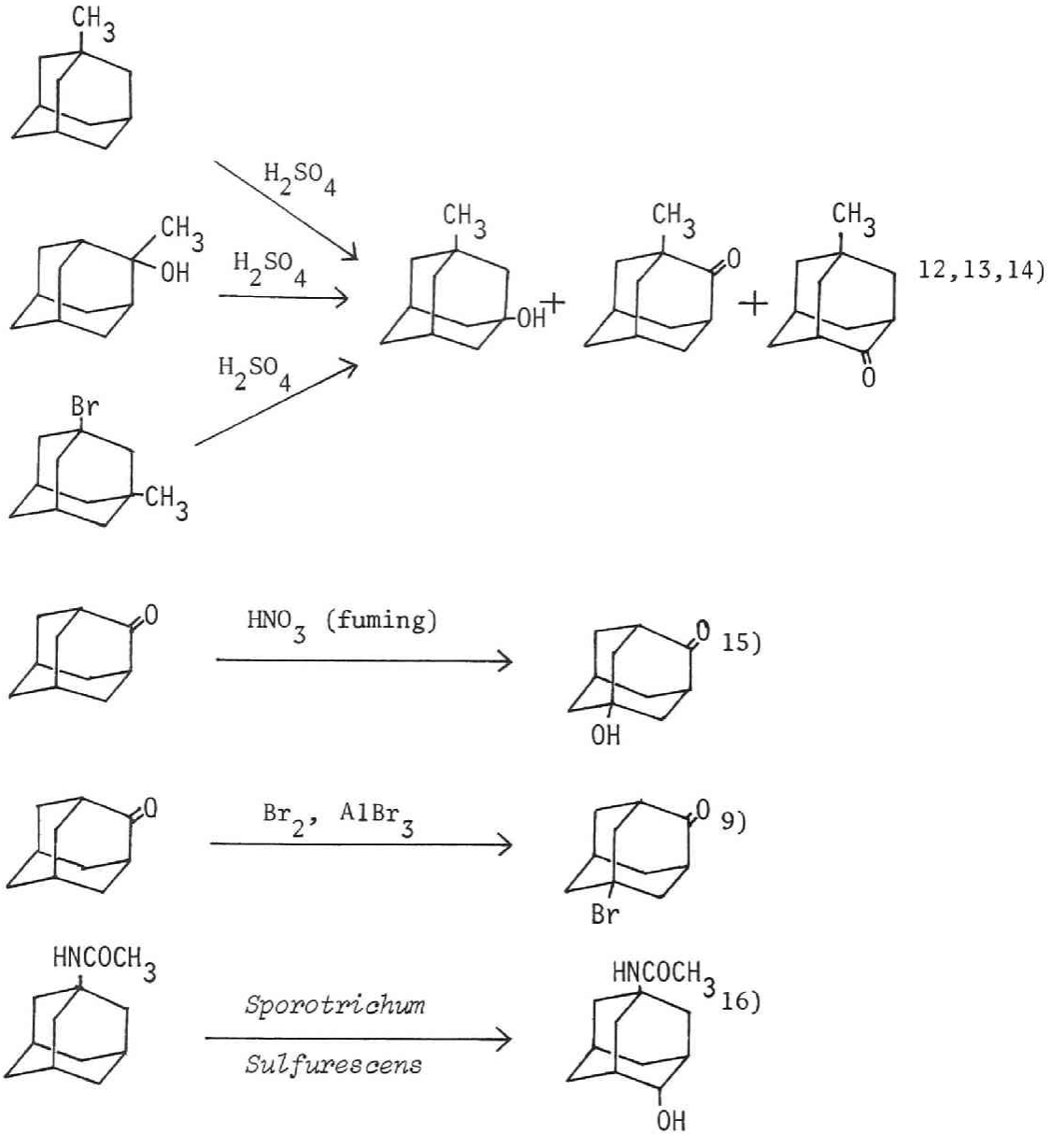








difunctionalization of adamantane. The sulfuric[12,13,14] or nitric acid[15] oxidation or oxidative rearrangement of 1- or 2-adamantyl derivatives gave some 1,4-disubstituted adamantanes.



The aluminum bromide catalyzed bromination of adamantanone has been reported to give 1-bromoadamantan-4-one almost exclusively.[9] A unique microbiological oxidation of 1-acetamido or benzamido-adamantane has been reported to give the anti 4-hydroxy derivatives.[16) 6)]

The present chapter described the preparations of 1,2- and 1,4-disubstituted adamantanes utilizing some novel together with known techniques.

1.3 Results and Discussion

Preparations of Some 1,2-Disubstituted Adamantanes Derived from 1-Carboxyadamantan-2-one (1).

1-Carboxyadamantan-2-one (1) was prepared by a modification of the procedure of Peters. et al.[17] (Chart I). The modification was made for the preparation of homoadamantanone, which was obtained by the hydrolytic rearrangement of 1-dichloromethyladamantane[2] in our study instead of diazomethane ring homologation of adamantanone.

Some 1,2-disubstituted adamantanes derived from the ketoacid (1) are summarized in Chart II. Sodium borohydride reduction of the ketoacid (1) gave, in a quantitative yield, the oxyacid (2), which was esterified with diazomethane in a quantitative yield.

Some unexpected difficulties have been encountered in the next step, the replacement of the hydroxy to bromine giving the bromoester (4). Common procedures such as treating the oxyester (3) with thionyl bromide or triphenylphosphine dibromide did not give satisfactory results. In analogy with the successful chlorination of an alcohol by dichlorocarbene in an alkaline emulsion,

Chart I

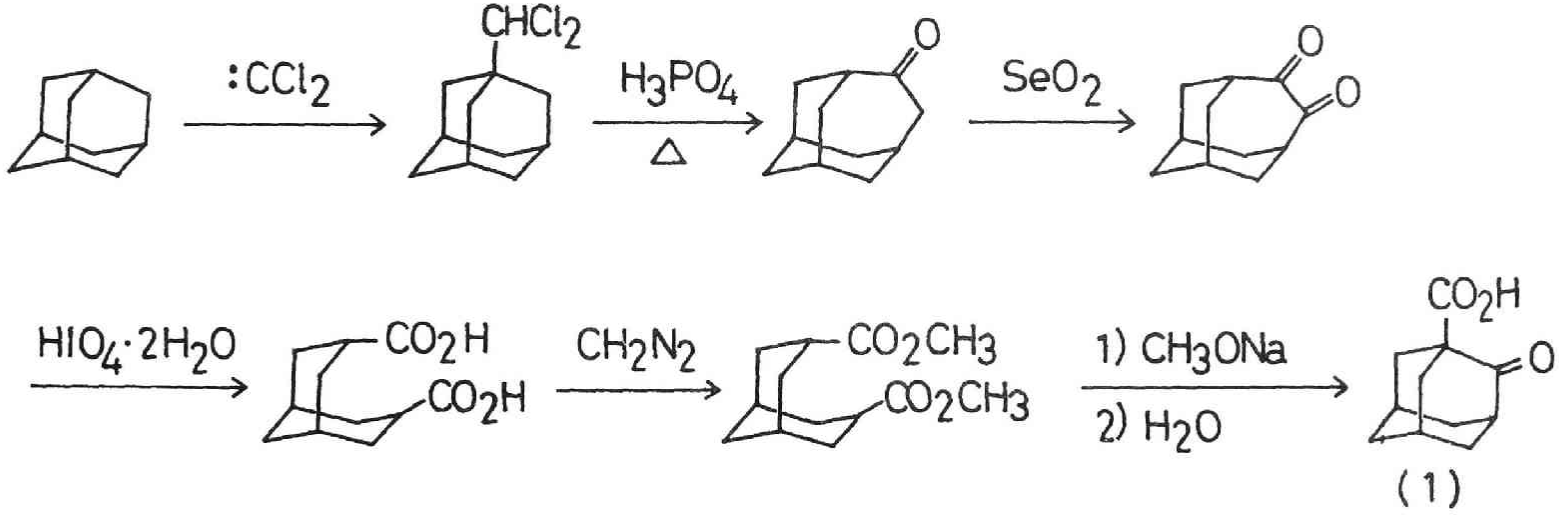
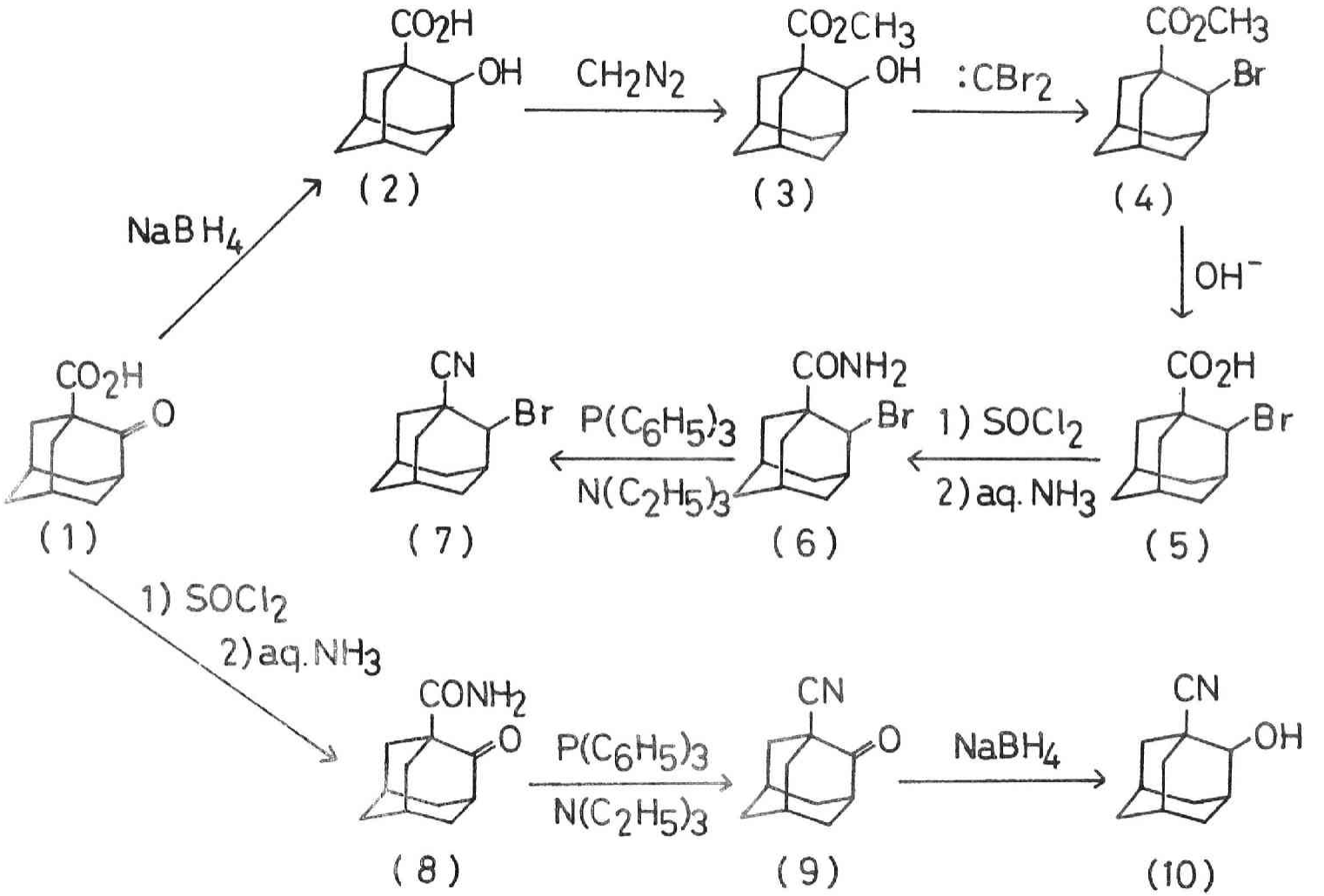
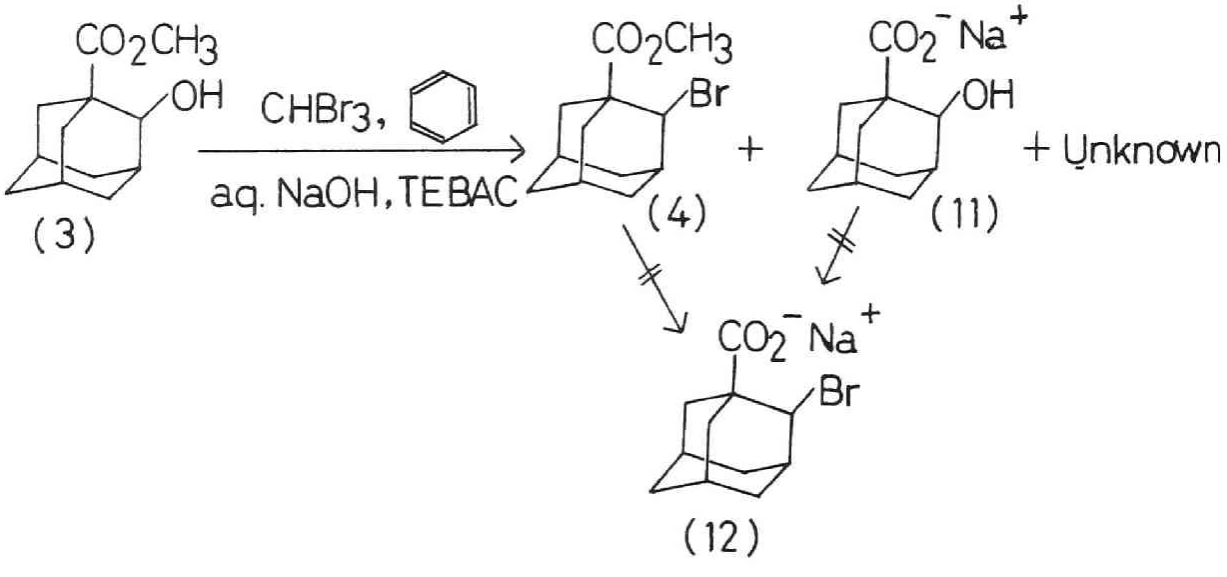

:CCl2
CHCl2
H3PO4
△
O
SeO2
O
O
HIO4·2H2O
CO2H
CO2H
CH2N2
CO2CH3
CO2CH3
1) CH3ONa
2) H2O
CO2H
O
(1)

Chart II


CO2H
OH
CH2N2
CO2CH3
OH
:CBr2
CO2CH3
Br
(2)
(3)
(4)
NaBH4
OH⁻
CO2H
O
CN
Br
P(C6H5)3
N(C2H5)3
CONH2
Br
1) SOCl2
2) aq. NH3
CO2H
Br
(1)
(7)
(6)
(5)
1) SOCl2
2) aq. NH3
CONH2
O
P(C6H5)3
N(C2H5)3
CN
O
NaBH4
CN
OH
(8)
(9)
(10)

the dibromocarbene bromination of the alcohol was the final choice for this conversion. Thus, the reaction of the oxyester (3) with dibromocarbene generated from bromoform in 50 % aqueous sodium hydroxide containing a small amount of benzene emulsified by triethylbenzylammonium chloride (TEBAC) gave the expected bromoester (4) (10-15% yield) together with unknown tarry materials and the hydrolyzed oxycarboxylate (11), which was subjected to a cycle of reesterification-dibromocarbene bromination to complete the conversion.



Interestingly, there was found no bromocarboxylate (12), suggesting that neither the hydrolysis of the bromoester (4) nor the bromination of the oxycarboxylate (11) took place under the present condition.

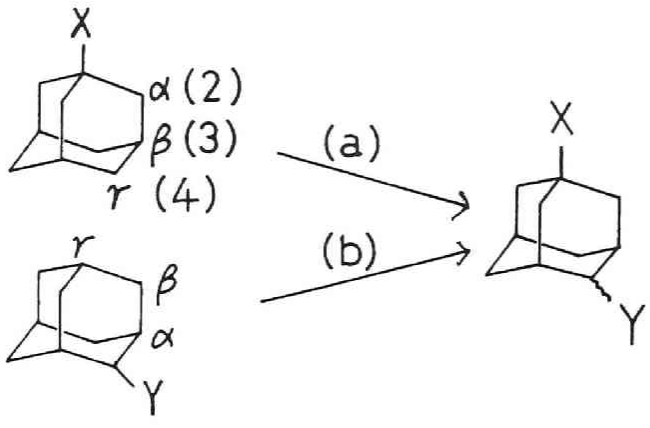
The bromoester (4) was hydrolyzed to the bromoacid (5), which was converted to the bromoamide (6) via the acid chloride in a 60 % yield. Finally was obtained the bromonitrile (7) by the triphenylphosphine-triethylamine dehydration of the bromoamide (6) *)

Similarly were obtained the ketoamide (8) in a yield of 73% and the ketonitrile (9) in a yield of 85% starting from the ketoacid (1). Sodium borohydride reduction of the ketonitrile (9) gave the oxynitrile (10) in a yield of 99%.

Preparation of 1-Acetyl-4-acetoxyadamantane and Derived Compounds.

Principally, a 1,4-disubstituted adamantane may be prepared either by a selective γ (bridge) substitution of a 1-substituted adamantane (process a) or by a selective γ (bridgehead) substitution of a 2-substituted adamantane (process b). Process a would be less accessible, for even in the free radical substitution of a 1-substituted adamantane, attack at the γ (4)

(*) The procedure was practically the same as that of Snatzke [19] for the preparation of 4-cyano-2,6-adamantanedione.



position was the minor reaction compared with the attack at the β (3) position[20] and the stereoselectivity in the atom transfer step to thus formed γ (4) radical was very low*)

Process b, on the other hand, seems more promising because of a number of known examples of selective bridgehead substitutions such as many ionic substitutions[1] dichlorocarbene insertion[2], and photoacetylation[3].

(*) Nearly 1:1 stereoisomer ratio of 1,4 syn and 1,4 anti products were obtained in the NBS bromination of 1-tert-butyladamantane or the chlorocarbonylation of 1-methyl-adamantane. I. Tabushi, Y. Aoyama, and T. Okada, unpublished results.

The nonionic*) regioselective γ substitution of a 2-substituted adamantane was realized, for the first time, for 2-acetoxyadamantane in the photoacetylation,which was originally applied to adamantane to give rise to an exclusive formation of bridgehead acetyladamantane and was characterized by hydrogen abstraction by the photoexcited biacetyl triplet followed by the acetyl transfer from biacetyl to thus formed adamantyl radical[3].

High pressure mercury lamp irradiation of a methylene chloride solution of 2-acetoxyadamantane and excess biacetyl resulted in the formation of, besides a large amount of the unreacted materials and undesired biacetyl derived products, two bridgehead acetylated products (13s and 13a) (ca. 10% after purification based on used 2-acetoxyadamantane, more than 40% based on consumed 2-acetoxyadamantane[26]) in a ratio of ca.1.7:1, although it was not yet decided which was which. That no appreciable bridge acetylation had took place was confirmed by the lack of signal assignable to the α proton of acetyl in the nmr spectra, in accord with

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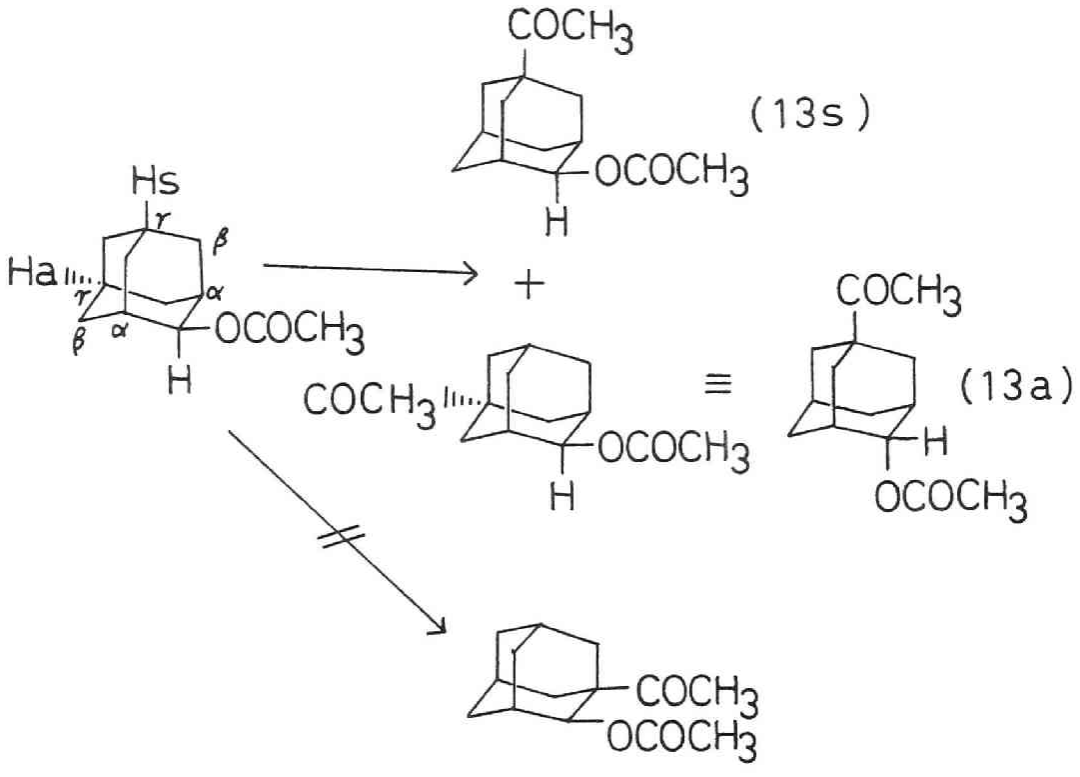
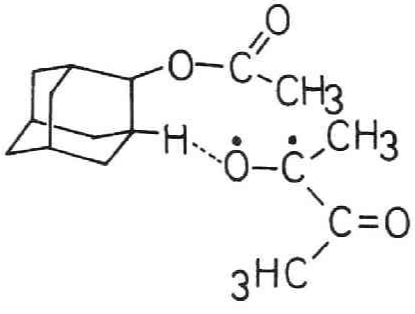
(*) Almost regioselective γ bromination (ionic) of adamantanone was reported[9]. Free radical bromination of adamantanone, however, was less selective, giving all possible monobromoadamantanones[21].



the photoacetylation of adamantane[3]. The acetyl acetates (13s and 13a); nmr (CCl_4, TMS), sharp singlet at τ 8.00 (acetyl and acetoxy) and a broad singlet at τ 5.22 (acetoxy methine), ir 1705 cm^{-1} (acetyl) and 1740 cm^{-1} (acetoxy). The acetyl acetates were converted to the oxyester (15) (Chart III), different from the known 2-oxy-1-carbomethoxyadamantane (3).

On this basis, it was concluded that the present photoacetylation took place exclusively at the γ bridgehead. This result may interestingly be compared with the less selective free radical halogenation of adamantanone ethylene-ketal[22], 2,2-dimethyladamantane[22], or adamantanone[21], where the γ to α reactivity ratio ranged from 4 to 9. Although the electronic effect of the acetoxy group can never be neglected, the steric repulsion between the acetoxy group and the bulky photoexcited biacetyl in the hypothetical transition state of



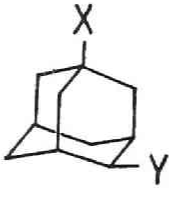
the α hydrogen abstraction may be the best candidate for the origin of the observed high selectivity of γ-acetylation. This viewpoint is in accord with the conclusion

drawn about the photoacetylation of adamantane derivatives including diamantane[23].

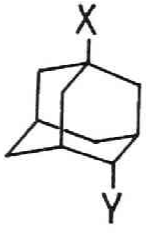
Contrary to the above described high regioselectivity, a modest selectivity was observed for the abstraction of two kinds of γ hydrogens, one (Hs) which was syn to the acetoxy and the other (Ha) which was anti to the acetoxy. Abstraction of Hs or Ht would lead to the syn (13s) or anti (13a) acetylacetoxy derivative , respectively. This kind of "stereoselectivity" will be discussed after the structural assignment is completed.

Some 1,4-disubstituted adamantanes derived from the acetyl-acetoxyadamantane (13) are summarized in Chart III.

Because it was not successful to separate the two stereoisomers (13s and 13a) in a preparative scale, all of the derived compounds (14-20) were obtained as mixtures of 1,4 syn and 1,4 anti derivatives.

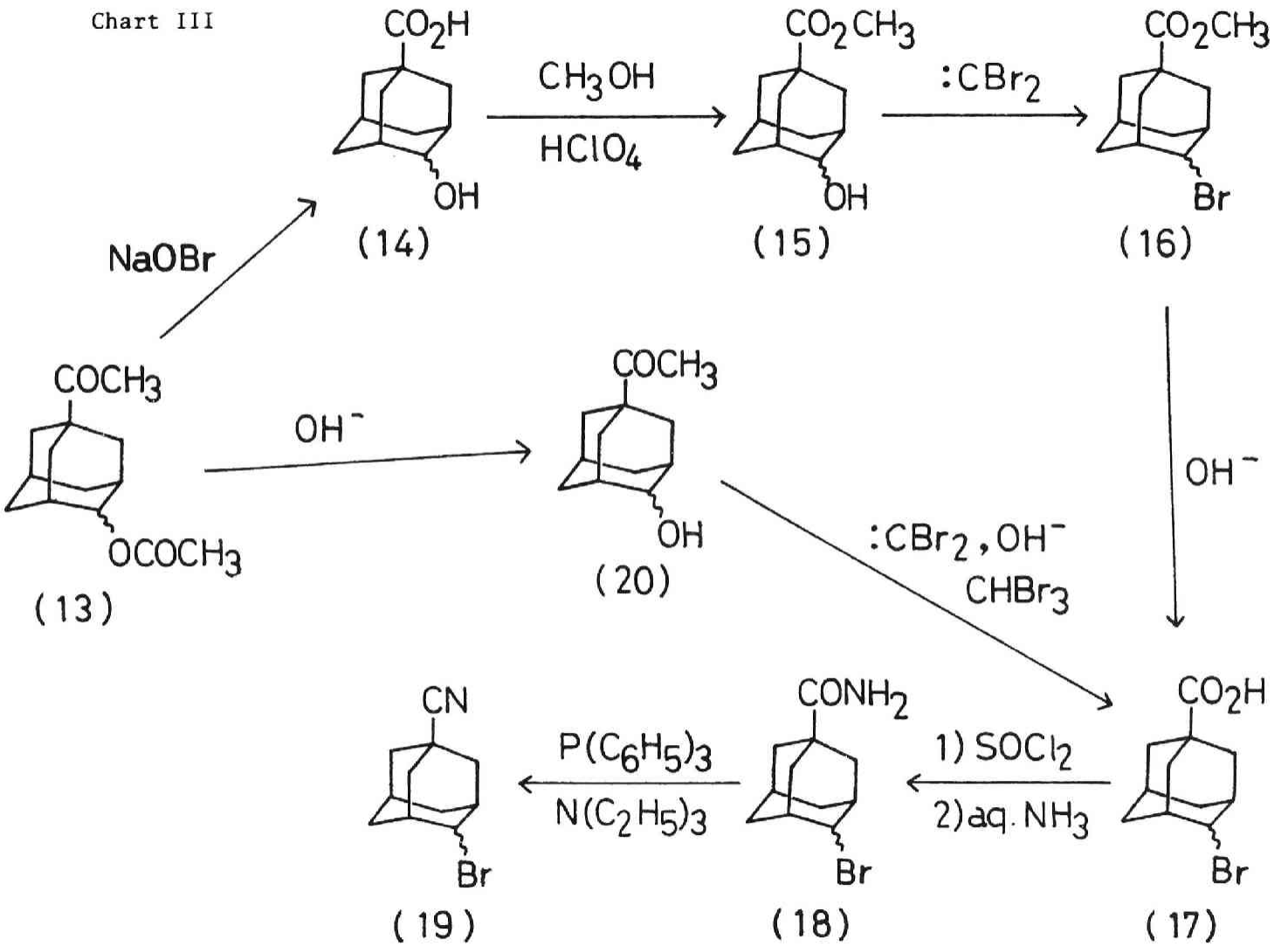


1,4 syn



1,4 anti

Chart III


CO2H
OH
(14)
CH3OH
HClO4
CO2CH3
OH
(15)
:CBr2
CO2CH3
Br
(16)
NaOBr
COCH3
OCOCH3
(13)
OH⁻
COCH3
OH
(20)
:CBr2, OH⁻
CHBr3
OH⁻
CN
Br
(19)
P(C6H5)3
N(C2H5)3
CONH2
Br
(18)
1) SOCl2
2) aq. NH3
CO2H
Br
(17)

The bromoform reaction of acetylacetoxyadamantane (13) in dioxane-water gave the oxyacid (14) in a 50 % yield, which was quantitatively esterified to the oxyester (15) and then converted to the bromoester (16) via the dibromocarbene bromination in a yield of ca. 20 %. The dibromocarbene bromination was accompanied with the appreciable hydrolysis of the starting ester. The bromoacid (17), bromoamide (18), and bromonitrile (19) were obtained in similar ways as their 1,2 counterparts (5,6, and 7).

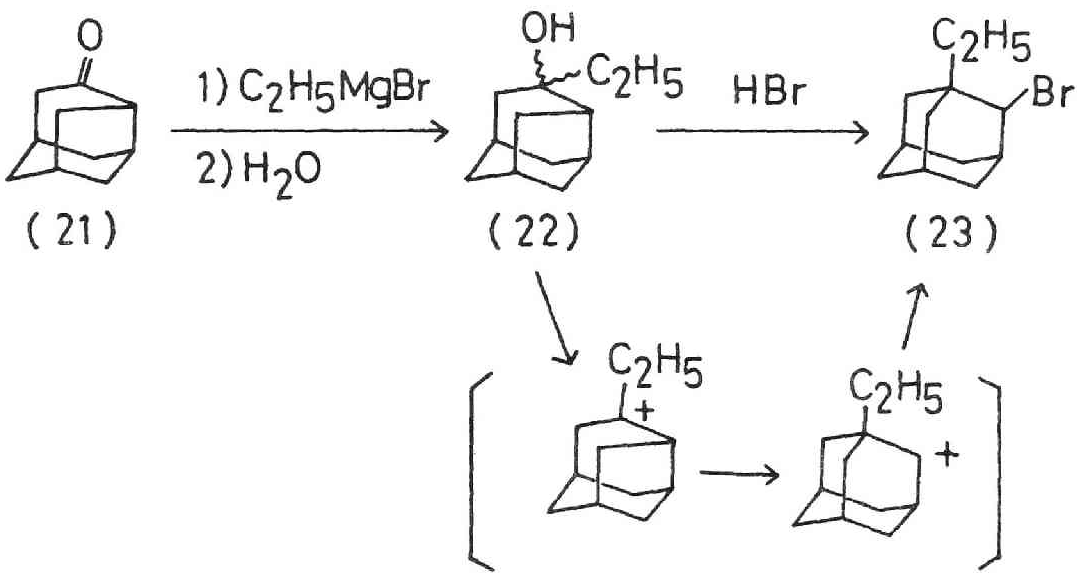
Interestingly, the dibromocarbene bromination of 4-oxyacetyladamantane (20) obtained in a yield of 84 % by the hydrolysis of acetylacetoxyadamantane (13) gave the bromoacid (17) in a yield of 37 %. The observed conversion of acetyl to carboxyl seems to be the result of the bromoform reaction or some unknown reaction of this kind.

Glpc separation of 1,4 syn and 1,4 anti isomers was satisfactory for the bromoester (16) and bromonitrile (19), where the observed stereoisomer ratios were ca. 2:1 and ca. 1:1, respectively, which were somewhat larger or smaller than the stereoisomer ratio of 1.7:1 of acetylacetoxyadamantane (13).

Preparation of 1-Ethyl-2-bromoadamantane via the Protoadamantane Route.

1-Ethyl-2-bromoadamantane (23) was prepared via the proto-

Chart IV

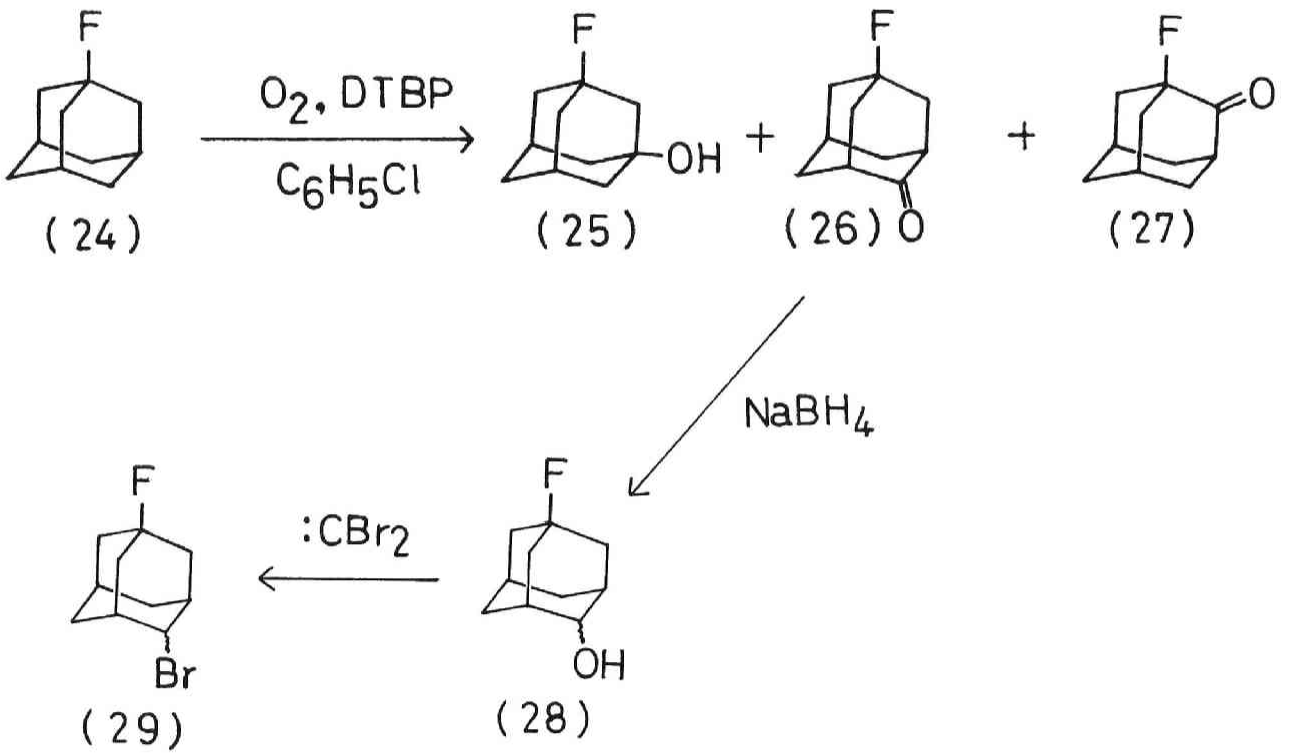


adamantane route[6] (Chart IV). Thus, readily available 4-protoadamantanone (21)[24] was converted in a 91% yield to the ethylhydroxy derivative (22) by the reaction with ethylmagnesium bromide. Treatment of 22 with etheral hydrogen bromide resulted in the formation of 1-ethyl-2-bromoadamantane (23) (61%).

Di-tert-butyl Peroxide Initiated Autoxidation of 1-Fluoroadamantane.

Autoxidation of 1-fluoroadamantane (24) in chlorobenzene was carried out using di-tert-butyl peroxide as an initiator under the vigorous flow of oxygen at 110-120°. As oxidates, there were obtained 1-fluoroadamantan-3-ol (25), 1-fluoroadamantan-4-one (26), and 1-fluoroadamantan-2-one (27) (in the order of glpc elution from a silicone column) in a ratio of ca. 6:2:1 (Chart V), which were readily separated by means of a silica gel column chromatography. The order of the glpc elution of the two ketones (26 and 27) was as expected from that of the corresponding 1,2- and 1,4-bromoadamantanones[21]. The expected upfield shift of the carbonyl stretching frequency of the 2-ketone (27, 1750 cm^{-1}) compared with that of the 4-ketone (26, 1740 cm^{-1}) was a further support for these structural assignment. From the major ketone (26) was obtained the oxyfluoride (28) by the sodium borohydride reduction in DMF (87%). The dibromocarbene bromination of the oxy fluoride (28) gave the fluoro bromide (29) in 45% yield.

Chart V



(24) (25) (26) (27) (28) (29)

Except for some regioselective substitutions such as dichlorocarbene insertion or photoacetylation, more common free radical substitutions are not recommendable for the second (or further) functionalization because of the low selectivities of attacking radicals resulting in the formation of tedious-to-separate mixtures of isomers[20,*]. A synthetic merit of the oxidation of a substituted adamantane lies in the ease with which the isomeric products are separated, i.e., the bridgehead attack leads to an alcohol, whereas the bridge attack leads to a ketone. Thus, despite of low selectivity, autoxidation may, sometimes, still be an effective procedure for the preparations of adamantane derivatives such as fluoroadamantanones which, otherwise, are less accessible.

α Methine Proton Chemical Shifts of 1,2- and 1,4-Disubstituted Adamantanes...

Because of its rigidity, adamantane may be one of the most ideal model for the investigation of the effects of a substituent on the chemical shifts of protons which are fixed at definite angle and distance from a substituent. Especially interesting

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(*) Perfect determination of the free radical bromination of 1-substituted adamantanes will be described in chapter 7.

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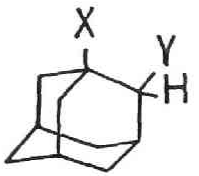
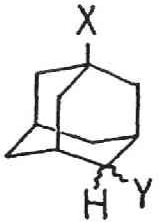
problem would be whether or not the effects of substituents are additive in di- or polysubstituted adamantanes. The nmr spectra of bridgehead polysubstituted adamantanes [25] and 2,4-disubstituted adamantanes [26] have been studied along this line.

For a 1,2 or 1,4 derivative , a characteristic absorption of the α methine (geminal to the 2- or 4- substituent) proton was easily detected and is shown in Table I. The nmr spectrum of a 1,4 derivative except the oxyfluoride (28) showed single α proton absorption with some broadening, although a 1,4 derivative was actually obtained, as mentioned earlier, as a mixture of 1,4 syn and 1,4 anti isomers. This result was in accord with the fact that no appreciable difference was observed in the chemical shifts of 4-axial and 4-equatorial protons of a 1-substituted adamantane.[25] In Table I are also shown the chemical shifts predicted from the additivity relationship based on the chemical shifts of monosubstituted adamantanes.[25] A marked difference in 1,2- and 1,4-disubstituted adamantanes may easily be seen in Table I. Without exception, the α methine proton chemical shifts of all of the 1,4-disubstituted adamantanes examined could be reproducible within 0.05 ppm by the additivity relationship, whereas such an additivity rule did no longer hold for 1,2-disubstituted derivatives, especially for 1-cyano-2-bromo-adamantane, where a deviation as large as 0.35 ppm was observed.

Table I. Chemical Shifts of the α Methine Protons of Some 1,2- and 1,4-Disubstituted Adamantanes [a]



X	CH_3	CH_3	C_2H_5	CO_2H	CO_2CH_3	CO_2CH_3	Cl	CN	CN
Y	OH	Br	Br	OH	OH	Br	Cl	OH	Br
Chemical Shift (τ)									
Obsd	6.52[b,c]	5.60[b,c]	5.67	5.90[b]	6.02	5.33	5.50[b,c] 5.65[b,e]	6.10	5.50
Predicted	6.42[d]	5.63[d]	5.72	5.96[d]	6.10	5.34	5.23[d]	5.90	5.15



X	$COCH_3$	$COCH_3$	CO_2CH_3	CO_2CH_3	Cl	F	CN
Y	$OCOCH_3$	OH	OH	Br	Cl	OH	Br
Chemical Shift (τ)							
Obsd	5.22	6.23	6.23	5.51	5.72[b,f,g]	6.32[f]	5.47
Predicted	5.26	6.18	6.27	5.51	5.69[d]	6.36	5.45

a) In carbon tetrachloride with TMS as a standard.

b) In deuterochloroform.

c) Reference 6b.

d) Calculated from the substituent shifts in deuterochloroform.

e) Reference 6a.

f) Avarage of the chemical shifts of 1,4 syn and 1,4 anti isomers.

g) Reference 14.

1,2-Disubstituted derivatives having less electron withdrawing groups such as alkyl or carbomethoxy had the α methine proton chemical shifts predictable from the additivity rule. Although only a limited sets of substituents allows no decisive conclusion, a success or a failure of the additivity rule prediction about the α methine proton chemical shift of a 1,2-disubstituted adamantane may be dependent on the nature of the 1-substituent (alkyl, carbomethoxy, halo, or cyano) rather than on that of the 2-substituent (hydroxy or bromine).

Contrary to the bridgehead polysubstituted adamantanes,[25] it was reported[26] that the α methine proton chemical shifts of some 2,4-disubstituted adamantanes were not predictable from the substituent shift additivity. No reasonable explanation, however, was made anywhere. Although we also hesitate to present a full interpretation of the present results, some specific interaction (steric or electronic) between the 1- and 2-substituents may be responsible for the failure of the additivity rule prediction about the α methine proton chemical shifts of some 1,2-disubstituted adamantanes.

1.4 Experimental

General.— Melting points (sealed capillary) and boiling points were uncorrected. Ir spectra were obtained with Hitachi 215 spectrophotometer. Unless otherwise indicated, nmr spectra were taken in carbon tetrachloride with TMS and were recorded with Varian T 60 spectrometer. Mass spectra were obtained with Hitachi mass spectrometer. Microanalyses were performed either at the Microanalysis Center of Kyoto University or at the Faculty of Pharmaceutical Science of Kyushu University.

1-Carboxyadamantan-2-one (1).— According to the procedure of Peters, et al.,[17] 1 was prepared from homoadamantanone via four steps (selenium dioxide oxidation, periodic acid oxidative cleavage, esterification, and ester condensation followed by hydrolysis). Homoadamantanone was obtained by the hydrolytic rearrangement in polyphosphoric acid of 1-dichloromethyladamantane[2], which was prepared by the dichlorocarbene insertion into adamantane in an emulsifying system[2].

1-Carboxyadamantan-2-ol (2).— A mixture of 2.93 g of 1 and 320 mg of sodium borohydride in 10 ml of DMF was stirred for 1 hr in an ice bath and then for 18 hr at room temperature. The most of the DMF was removed in vacuo (140 mmHg) and, after acidification with hydrochloric acid, the mixture was extracted with three portions of 100 ml of ether. The combined ether extract was washed

with water and dried over sodium sulfate. Evaporation of ether gave 2.96 g (quantitative) of 2 as a white solid : mp 125.5-126.5° (from 30% aqueous methanol); ir (KBr) 3345, 1705, 1280, 1252, 1208, and 1046 cm^{-1}; nmr ($CDCl_3$) τ 2.43 (broad s, 2H, CO_2H and OH, disappeared on deuteration), 5.90 (broad s, 1H, CHOH), and 7.6-8.6 (m, 13 H, remaining adamantyl protons)

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.21. Found: C, 67.31; H, 8.19.

1-Carbomethoxyadamantan-2-ol (3).— To 800 mg of 2 was added an ether solution of excess diazomethane. The solution was stirred for 1 hr at room temperature. Evaporation of ether and excess diazomethane gave an oil which was distilled at 114-115°/0.4 mmHg to give 3 in an almost quantitative yield: ir (neat) 3500, 1735, 1245, 1105, 1080, and 1053 cm^{-1}; nmr τ 6.02 (broad s, 1H, CHOH), 6.33 (s, 3H, CH_3), ca. 6.4 (broad s, 1H, OH, disappeared on deuteration), and 7.7-8.6 (m, 13H, remaining adamantyl protons); mass spectrum m/e (relative intensity) 210 (M^+, 3.5), 192 (4.3), 182 (36), 151 (36), and 150 (100).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.61; H, 8.84.

1-Carbomethoxy-2-bromoadamantane (4).— To a vigorously stirred mixture of 2.7 g of 3, 7 ml of benzene, 60 ml of 50 % (wt/wt) aqueous sodium hydroxide, and 400 mg of triethylbenzylammonium chloride were added at room temperature 25 ml of bromoform in a

period of 2 hr. The mixture was stirred for further 2 hr, then 30 ml of water was added and the mixture was extracted with five portions of 70 ml of ether. Usual work-up (washing, drying, and evaporation) on the ether extract gave a brown tarry material (1.9 g), which was chromatographed on a silica gel column. Elution with benzene-hexane (1:1) gave an yellow oil (0.96 g) which was distilled at 115-120°/0.3 mmHg to give 360 mg (10 %) of 4: ir (neat) 1750, 1255, and 1092 cm^{-1}; nmr τ 5.33 (broad s, 1H, CHBr), 6.36 (s, 3H, CH_3), and 7.4-8.4 (complex m with peaks at 7.60, 7.77, 8.03, and 8.30, 13 H, remaining adamantyl protons); mass spectrum m/e 272 and 274 (M^+, 27.6), 241 and 243 (3.5), 213 (11), and 193 (100).

Anal. Calcd for $C_{12}H_{17}O_2Br$: C, 52.77; H, 6.27. Found: C, 52.63; H, 6.04.

Further elution with benzene gave a tarry material (ca. 1 g), the nmr spectrum of which showed no methyl signal. The structure was not further investigated.

The aqueous layer was acidified with hydrochloric acid and then extracted with three portions of 30 ml of methylene chloride. After evaporation of methylene chloride, the residue was esterified as above. Glpc analysis showed a single peak which was identified as the starting material (3) by means of glpc coinjection and spectral behavior. Thus recovered oxyester (3) was further subjected to the dibromocarbene bromination.

1-Cyano-2-bromoadamantane (7).— A mixture of 159 mg of 4 and 80 mg of powdered sodium hydroxide in 20 ml of methanol containing 1 ml of water was refluxed for 5 hr. At the end of the reaction, 70 ml of water was added and the mixture was extracted with ether. From the ether extract was recovered a small amount of the unreacted ester. The alkaline layer was acidified with hydrochloric acid and extracted with methylene chloride. Drying and evaporation gave 100 mg (69 %) of 1-carboxy-2-bromoadamantane (5) as an oil, which was dissolved in 2 ml of thionyl chloride. The mixture was refluxed for 2 hr, then thionyl chloride was evaporated in vacuo and the residue was dissolved in 0.5 ml of dry tetrahydrofurane. The tetrahydrofurane solution was added to 3 ml of 28 % aqueous ammonia with stirring. The mixture was stirred at room temperature for 1 hr and extracted with methylene chloride. From the methylene chloride extract was obtained 61 mg (61 % from 5) of 1-carbamoyl-2-bromoadamantane (6): ir 1680 cm^{-1}. A solution of 30 mg of crude 6, 60 mg of triphenylphosphine, 0.046 ml of triethylamine, and 35 mg of carbon tetrachloride in 3 ml of methylene chloride was refluxed for 15 hr. Water was added and the mixture was shaken. The organic layer was dried over sodium sulfate and evaporated to dryness and the residue was chromatographed on a silica gel column. After elution with hexane, 7 was eluted with hexane-benzene (1:1). Pure 7 was obtained by means of preparative glpc (Silicone DC 550): ir (KBr)

2250, 970, and 735 cm^{-1}; nmr τ 5.50 (broad s, 1H, CHCN), 7.5-8.5 (complex m with peaks at 7.60, 7.79, 8.05, and 8.30, 13H, remaining adamantyl protons), mass spectrum m/e 239 and 241 (M^+, 2.35) and 161 (100).

1-Carbamoyladamantan-2-one (8).— A solution of 850 mg of 1 in 10 ml of thionyl chloride was refluxed for 2 hr, then excess thionyl chloride was removed in vacuo. The residue was dissolved in 6 ml of dry tetrahydrofurane and the tetrahydrofurane solution was added dropwise at 0° to 12 ml of 28 % aqueous ammonia with stirring. Stirring was continued for 3 hr at room temperature. Water was added and the mixture was extracted with methylene chloride. The extract was dried over sodium sulfate and evaporated to dryness to give 620 mg (73 %) of 8: mp 177-177.5° (from cyclohexane); ir (KBr) 3425, 3345, 3293, 3195, 1713, 1663, 1619, and 1056 cm^{-1}; nmr ($CDCl_3$) τ 2.0-2.5 and 3.8-4.6 (very broad, each corresponded to 1H, NH_2, disappeared on deuteration), and 7.2-8.3 (m with peaks at 7.38, 7.60, and 7.90, 13H, adamantyl protons); mass spectrum m/e 193 (M^+, 8.0), 164 (27.0), and 150 (100).

Anal. Calcd for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.14; H, 8.01; N, 7.23.

1-Cyanoadamantan-2-one (9).— Practically the same procedure for the preparation of 7 was applied to 8 to give 9 in a yield of 85 %: mp 199.5-200.5° (from cyclohexane); ir (KBr) 2250, 1730, and 1062 cm^{-1}; nmr ($CDCl_3$+CCl_4) τ 7.32 (broad s, 1H, bridgehead

proton vicinal to C=O), 7.67 (broad s, 4H, methylene protons vicinal to CN), and 7.7-8.2 (m, 8H, remaining adamantyl protons) ; mass spectrum m/e 175 (M^+, 51.8), 149 (22), 147 (100), and 146 (23.2)

Anal. Calcd for $C_{11}H_{13}ON$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.50; H, 7.23; N, 7.75.

1-Cyanoadamantan-2-ol (10).— A mixture of 300 mg of 9 and 35 mg of sodium borohydride in 10 ml of DMF was stirred at room temperature for 20 hr. Usual work-up gave 300 mg (99 %) of 10 as a white crystal: mp 215.5-216° (from cyclohexane); ir (KBr) 2234, 1102, 1056, and 1031 cm^{-1}; nmr τ 6.10 (broad s, 1H, CHOH) and 7.4-8.5 (complex m with peaks at 7.43, 7.70, 7.99, 8.20, and 8.27, 14H, OH and remaining adamantyl protons); mass spectrum m/e 177 (M^+, 6.6), 150 (14.7), and 149 (100).

Anal. Calcd for $C_{11}H_{15}ON$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.68; H, 8.62; N, 7.81.

1-Acetyl-4-acetoxyadamantane (13).— A solution of 6.3 g of 2-acetoxyadamantane and 40 ml of biacetyl in 400 ml of methylene chloride was irradiated by a 450 W high pressure mercury lamp for 35 hr in an ice bath. The methylene chloride was removed in vacuo and the residue was distilled. Distillation at ca. 90° /3 mmHg gave an yellow to brown oil (ca. 13 g), which consisted mainly of 2-acetoxyadamantane and the pinacol derived from reductive dimerization of biacetyl.[27] About 5 g of 2-acetoxy-

adamantane was recovered by distillation after the removal of the pinacol via washing with water followed by adsorption on powdered calcium chloride. Further distillation at ca. 200°/3 mmHg gave an oil (4 g), which was washed with water. A large amount of powdered calcium chloride was added and the mixture was allowed to stand for 3 days. Distillation at 130-150°/0.4 mmHg gave an yellow oil (1.4 g), which was chromatographed on a silica gel column. About 600 mg of crude 13 was obtained by the elution with benzene. A pure sample for the analytic purpose was obtained by the preparative glpc followed by distillation: ir (neat) 1740 ($OCOCH_3$), 1705 ($COCH_3$), and 1260 cm^{-1}; nmr τ 5.22 (broad s, 1H, $CHOCOCH_3$), 8.00 (s, 6H, $COCH_3$ and $OCOCH_3$), and 7.8-8.4 (m, 13H, remaining adamantyl protons); mass spectrum m/e 236 (M^+, 5.3), 193 (85.6), 151 (100), and 133 (100).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.06; H, 8.39.

1-Carboxyadamantan-4-ol (14).— To a vigorously stirred solution of 2 g of sodium hydroxide and 1 ml of bromine in 12 ml of water was added a solution of 250 mg of 13 dissolved in 12 ml of dioxane in a period of 1 hr at 0°. The mixture was stirred at room temperature for 4 hr. Water (200 ml) was added and the mixture was extracted with ether. The alkaline layer was acidified with hydrochloric acid and extracted with methylene chloride. From the extract was obtained 110 mg (45 %) of 14: ir 1705 (broad).

1-Carbomethoxyadamantan-4-ol (15), 1-carbomethoxy-4-bromoadamantane (16), 1-carboxy-4-bromoadamantane (17), 1-carbamoyl-4-bromoadamantane (18), and 1-cyano-4-bromoadamantane (19).— These compounds were prepared by the similar procedures as described for the preparations of their 1,2 counterparts (3, 4, 5, 6, and 7).

15: ir (neat) 1737, 1250, and 1085 cm^{-1}; nmr τ 6.23 (broad s, 1H, CHOH), 6.40 (s, 3H, CH_3), and 7.7-8.4 (m, 14H, OH and remaining adamantyl protons); mass spectrum m/e 210 (M^+, 4.3), 192 (34), 151 (100), and 133 (81).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.32; H, 8.60.

16: ir (neat) 1735, 1250, 1080, and 733 cm^{-1}; nmr τ 5.51 (broad s, 1H, CHBr), 6.40 (s, 3H, CH_3), and 7.3-8.2 (m, 13H, remaining adamantyl protons); mass spectrum m/e 213 and 215 (12.5) and 193 (100).

Anal. Calcd for $C_{12}H_{17}O_2Br$: C, 52.77; H, 6.27. Found: C, 52.93; H, 6.14.

19: ir (KBr) 2270, 2250 (shoulder), 978, 925, and 740 cm^{-1}; nmr τ 5.47 (broad s, 1H, CHCN) and 7.3-8.5 (m with peaks at 7.7 and 8.1, 13H, remaining adamantyl protons); mass spectrum m/e 239 and 241 (M^+, 0.2) and 161 (100).

1-Acetyladamantan-4-ol (20).— A solution of 700 mg of 13 and 500 mg of powdered sodium hydroxide in 50 ml of methanol containing 1.5 ml of water was refluxed for half an hour. Water (300 ml) was added and the mixture was extracted with four portions of 30 ml of ether. The ether extract was washed with water and dried over sodium sulfate. Glpc analysis showed that the yield of 20 was 84 %. The ether was evaporated and the residue was distilled at 114-115°/0.4 mmHg to give 20: ir (neat) 3450, 1703, 1070, and 1040 cm^{-1}; nmr τ 6.23 (broad s, 1H, CHOH), 7.94 (s, 3H, CH_3), and 7.6-8.9 (complex m with peaks at 7.70, 8.23, 8.45, and 8.68, 14H, OH and remaining adamantyl protons), mass spectrum m/e 194 (M^+, 6.7), 151 (100), and 133 (52).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.33. Found: C, 73.83; H, 9.37.

Dibromocarbene Bromination of 20.— The reaction of 20 (270 mg) with dibromocarbene was carried out in a similar way as described for the preparation of 4. From the alkaline layer was obtained 130 mg (37 %) of 17.

4-Protoadamantanone (21)

According to the procedure of Lunn,[24] a mixture of 9.8 g of 1-adamantanol, 31.8 g of lead tetraacetate, 18.2 g of iodine, and 200 ml of dry benzene was stirred at 60° for 80 min. The cooled solution was filtered and the solid was washed with benzene and then with ether. The filtrate and washings were washed with aqueous

sodium bisulfite until colorless, with water, and then with dilute sodium bicarbonate, and dried. Evaporation at a temperature below 50° gave an oil which was crystallized from methanol at a dry ice-aceton temperature to give 8 g (44%0 of the iodiketone, ir 1700 cm^{-1}. The iodoketone (8 g) was stirred in pyridine (8 ml) at 55° for 4 hr. The cooled solution was poured into ice and the resulting solid was collected and recrystallized from methanol-water to give 3.3 g (77%) of 21, which was further recrystallized from pentane.

1-Ethyl-2-bromoadamantane (23).— To a 10 ml of ether solution of ethylmagnesium bromide prepared from 146 mg of magnesium and 670 mg of ethyl bromide was added a solution of 308 mg of 4-proto-adamantanone (21)[30] in 10 ml of ether. The mixture was refluxed for 2 hr. A saturated ammonium chloride solution (10 ml) was added and the ether layer was separated. The aqueous layer was extracted with 20 ml of ether. The combined ether extract was washed with water, dried over sodium sulfate and evaporated to give 335 mg (91 %) of 4-ethyl-4-hydroxyprotoadamantane (22) as an oil. No further purification was attempted on 22. A solution of 115 mg of 22 in 10 ml of ether saturated with hydrogen bromide was refluxed for half an hour. Evaporation of ether gave an oil, which was distilled to give 100 mg (61 %) of 23: ir (CCl_4) 962, 924, 890, 648, and 617 cm^{-1}; nmr τ 5.67 (broad s, 1H, CHBr), 7.58 (broad s, 1H, bridgehead proton adjacent to Br), 7.74 (broad

s, 2H, other bridgehead protons), 8.17, 8.27 (m, 10H, remaining adamantyl protons), 8.4-9.0 (2H, CH_2CH_3), and 9.0-9.4 (3H, CH_2CH_3) ; mass spectrum m/e 242 and 244 (M^+, 2.5), 213 and 215 (3.0), and 163 (100).

Anal. Calcd for $C_{12}H_{19}Br$: C, 59.27; H, 7.87. Found: C, 59.50; H, 8.04.

Autoxidation of 1-Fluoroadamantane.— A solution of 2.6 g of 1-fluoroadamantane (24) in 18 ml of chlorobenzene was heated at 120°. To this solution was added, under vigorous flow of oxygen, a mixture of 20 ml of di-tert- butyl peroxide and 8 ml of chlorobenzene in a period of 7 hr. The mixture was heated at the same temperature for 6 hr. After cooling, a small amount of ferrous oxide was added and the mixture was allowed to stand overnight. Chlorobenzene was distilled in vacuo (50 mmHg) and the residue was chromatographed on a silica gel column. Elution with pentane (300 ml) gave 343 mg of the recovered 1-fluoroadamantane. Elution with benzene (200 ml) gave white solid (350 mg), which consisted of 1-fluoroadamantan-4-one (26), 1-fluoroadamantan-2-one (27), and 1-fluoroadamantan-3-ol (25). Further elution with benzene (1000 ml) gave 25 (490 mg). The ketone fraction was rechromatographed on a silica gel column to complete the separation of 26 and 27 using hexane-benzene (1:1) as an eluent. By a controlled elution, there were obtained 27 mg of pure 27, 90 mg of pure 26, 80 mg of a mixture of these, and 150 mg of 25.

26: mp 170-171° (after sublimation in vacuo); ir (KBr) 1740, 1090, 1065, 1055, 965, and 920 cm^{-1}; nmr τ 7.40 (broad s, 2H, bridgehead protons adjacent to C=O) and 7.4-8.6 (m with peaks at 7.83, 8.06, and 8.30, 11H, remaining adamantyl protons); mass spectrum m/e 168 (M^+, 100), 149 (16.7), 140 (11.7), and 97 (100).

Anal. Calcd for $C_{10}H_{13}OF$: C, 71.40; H, 7.79. Found: C, 71.57; H, 8.06.

27: mp 213-216° (after sublimation in bacuo); ir (KBr) 1750, 1123, 1097, 1060, 970, 880, and 838 cm^{-1}; mass spectrum m/e 168 (M^+, 55.0), 149 (28.6), 140 (28.6), and 97 (100).

Anal. Calcd for $C_{10}H_{13}OF$: C, 71.40; H, 7.79. Found: C, 71.11; H, 7.75.

1-Fluoroadamantan-4-ol (28).— A mixture of 153 mg of 26 and 17 mg of sodium borohydride in 3 ml of DMF was stirred at room temperature for 15 hr, then 3 ml of water was added and the mixture was stirred for 10 min. Water was added and the product was extracted into three portions of 50 ml of ether. Washing, drying, and evaporation of the combined ether extract gave 133 mg (87 %) of 28: ir (KBr) 1103, 1078, 1057, and 910 cm^{-1}; nmr τ 6.23, 6.40 (broad s, 1H, CHOH), and 7.4-8.6 (m with peaks at 7.87, 8.20, and 8.36, 14H, OH and remaining adamantyl protons); mass spectrum m/e 170 (M^+, 8.7) and 151 (100).

1-Fluoro-4-bromoadamantane (29)

Dibromocarbene bromination of 1-fluoroadamantan-4-ol (28) was carried out similarly as described for the preparation of 4. 29 was obtained in a 45% yield as a white solid ; ir (KBr) 1357, 1087, 1060, 960, 915, 742, and 710 cm^{-1} ; nmr (CCl_4, TMS) τ 5.63 (1H, broad s, CHBr) and 7.3-8.5 (13H, m with a broad peak centered at 7.7 and a sharp peak at 8.18, remaining protons.

Anal. Calcd for $C_{10}H_{14}FBr$: C, 51.52; H, 6.24.

Found : C, 51.75; H, 6.03.

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Chapter 2

Preparation of Bromoadamantanones by Free Radical Bromination of Adamantanone

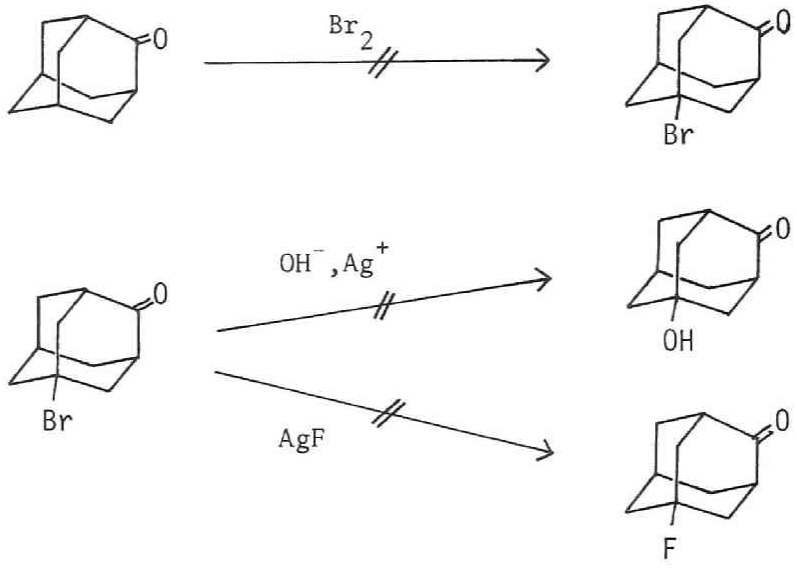
2.1 Summary

The free radical reaction of adamantanone and a brominating reagent (bromotrichloromethane, N-bromosuccinimide (NBS), or dibromomethane) in the presence of di-tert-butyl peroxide under nitrogen at 100-110° gave a mixture of bromoadamantanone regioisomers. The reaction took place preferentially at the C_γ position. The other bridgehead position, C_α, α to the carbonyl, had considerably reduced reactivity toward hydrogen abstraction. Stereoselective equatorial substitution on the C_β radical was also observed. Every bromoketone was fully characterized and spectral comparisons of regioisomers were made.

2.2 Introduction

Although adamantane readily gives a bridgehead derivative by an ionic substitution,[1] difficulties are usually experienced in the second introduction of a substituent by an ionic process into a 2-substituted adamantane. To overcome the serious electronic deactivation originating from an electronegative 2-substituent, drastic conditions are usually required, under which the 2-substituent itself may undergo undesired reactions. Inertness of adamantanone derivatives toward electrophilic reactions, which adamantane undergoes with much ease,

illustrates the situation, although bromination of adamantanone took place by use of a catalyst coupled with prolonged heating[2)]



In these circumstances, the free radical substitution may be another approach to the preparation of difunctional adamantanes. The electronic substituent effect should be less pronounced in free radical reactions[3)].

This chapter deals with the bromination of adamantanone, the first study of the free-radical substitution of polycyclic ketones as well as of 2-substituted adamantanes. Radical halogenation of an aliphatic ketone usually gives rise to an α substitution.[4)] An interest would be whether or not adamantanone, in which the α position is bridgehead, undergoes predominant α bromination. The effect of

the fixed orientation of bromine and carbonyl in the resulting bromoadamantanones on their chemical and physical properties may offer another interest.

2.3 Results and Discussion

The free radical bromination of adamantanone with bromotrichloromethane, N-bromosuccinimide (NBS), or dibromomethane was carried out under nitrogen at 100-110° in the presence of di-tert-butyl peroxide as an initiator. Besides products derived from a brominating reagents there were obtained five monobromoadamantanones (1,2,3,4, and 5 in the order of glpc elution from a poly (ethylene glycol) column), which were separated by means of column chromatography followed by preparative glpc. A typical gas chromatogram of the reaction mixture is shown in Figure 1.

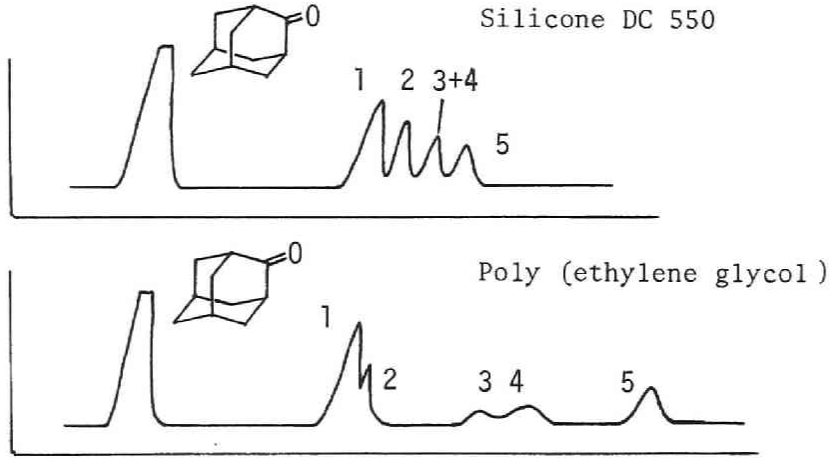
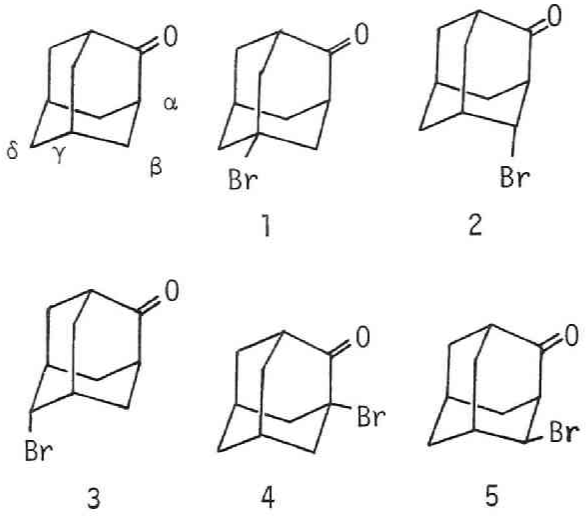


Figure 1. Gas chromatogram of the reaction mixture of bromination of adamantanone.



The structural assignments of bromo ketones were made by comparisons of their spectra with those reported in literature[5] and by chemical conversions to known compounds. The supposed structure of 4, which had not been reported in literature, was ascertained by its ir and nmr spectroscopic identity with the authentic 4 prepared by the Cristol modified Hunsdiecker reaction of 1-carboxyadamantanone -2.[6] Melting points and spectra of five bromo ketones are shown in Table I.

Table I. Melting points and Spectra[a] of Monobromoadamantanones

Compd	Mp,[b] °C (lit)	$\nu_{C=O}$, cm^{-1} (KBr)	λ_{max}, mμ (ε)[c] ($CHCl_3$)	Nmr, τ ($CDCl_3$, TMS)
1	153.5-156 (150-154[d])	1730[e]	294(16.6)	7.40(8H), 7.71(1H), 7.92(4H)[e]
2	159.5-161 (156-159[f])	1731[g] 1709[h]	298(75.0)	5.45(1H), 7.18(1H), 7.37(2H), 7.68 7.93 8.25(9H)[g]
3	186.5-188.5 (187-189[i])	1727 1704[h]	292(17.4)	5.24(1H), 7.17(1H), 7.39(3H), 7.78, 7.98, 8.23(8H)
4	124-125	1749[h] 1734	288(13.5)	7.03(1H), 7.40(4H), 7.95(8H)
5	156.5-159.5	1733[g]	292(28.5)	5.20(1H);[j] 7.08(1H), 7.40(2H), 7.70, 7.85, 8.11(9H)[g]

(a) Every bromo ketone showed the molecular peak at m/e 228 and 230 in its mass spectrum. (b) From hexane, sealed tube, uncorrected. (c) Adamantanone 291(24.2). (d) H. W. Geluk and J. L. M. A. Schlatmann, Tetrahedron, 24, 5369 (1968). (e) Similar spectrum was obtained.[d] (f) A. C. Udding, J. Strating, and H. Wynberg, Tetrahedron Lett., 1345 (1968). (g) Similar spectrum was obtained: G. Snatzke and G. Eckhardt, Chem. Ber., 101, 2010 (1968). (h) Shoulder. (i) M. A. McKervey, D. Faulkner, and H. Hamill, Tetrahedron Lett., 1971 (1970). (j) Quartet.

The carbonyl stretching frequencies may serve as instructive comparisons and are reproduced in Figure 2.

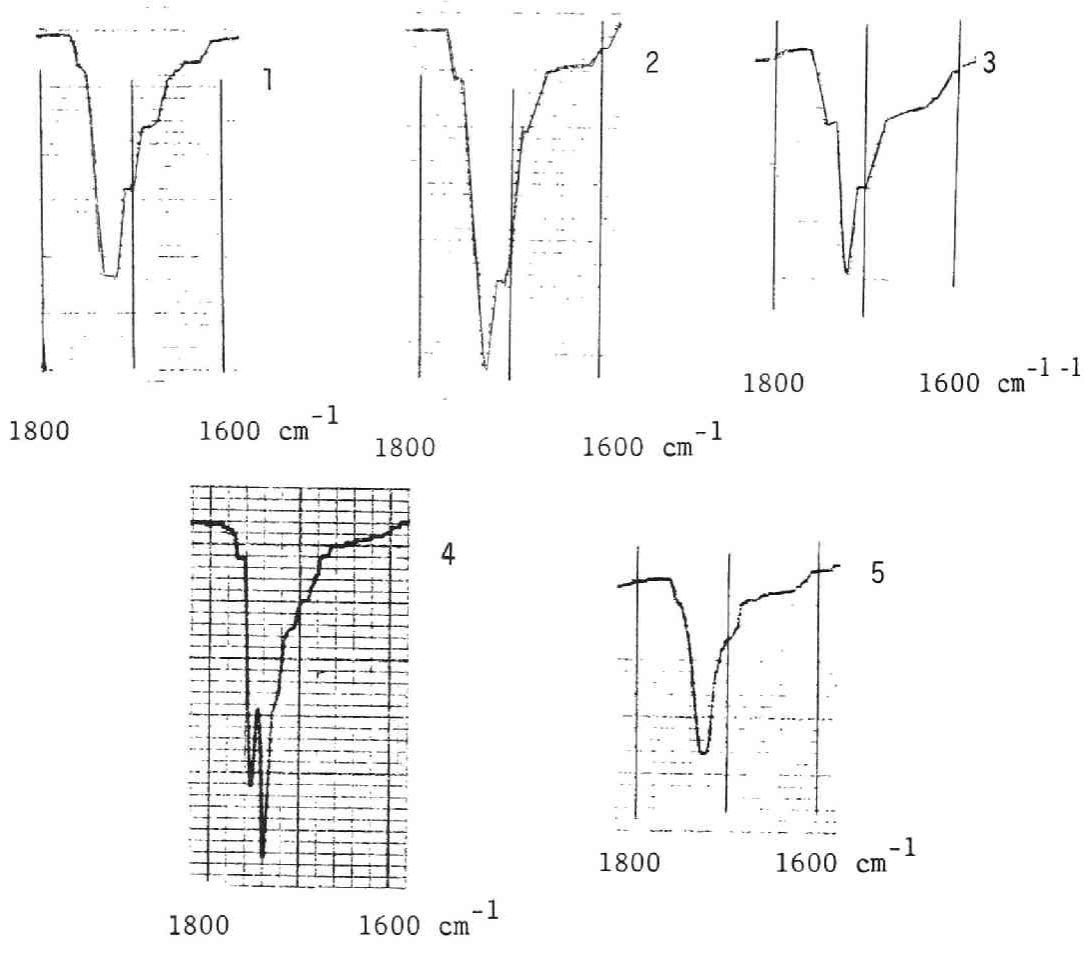
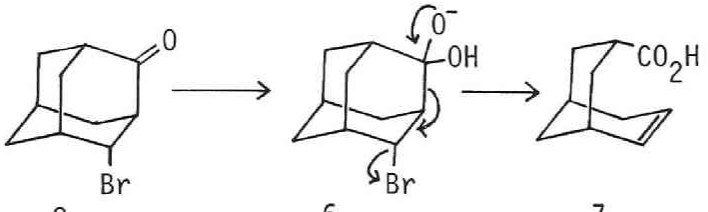


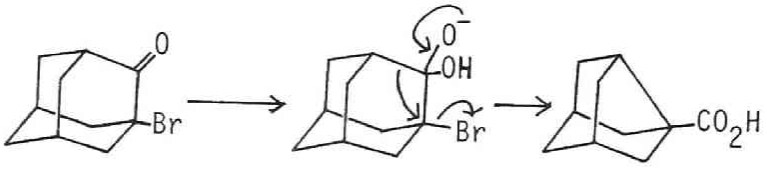
Figure 2. Carbonyl stretching absorptions of bromoadamantanones.

A moderate high-frequency shift by 24-9 cm^{-1} in $\nu_{C=O}$ and a small hypsochromic shift by 3 nm in λ_{max} of 4 observed are in good agreement with the reported ir and uv spectra of α(e)-bromocyclohexanone derivatives.[7] Interestingly, the bromine substitution always results in a high-frequency shift in $\nu_{C=O}$ irrespective of its location. A bathochromic shift by 7 nm and a considerable increase in molar extinction coefficiancy of 2 may be an evidence of a strong stereoelectronic interaction between bromine and carbonyl in 2 when it is taken into account that the stereo isomer 5 has practically the same uv spectrum as adamantanone.

The Favorskii (or quasi Favorskii) rearrangement was also useful to distinguish isomeric bromo ketones. On treatment with alkaline solution (potassium hydroxide in aqueous ethanol) only 2 and 4 were converted, as expected, to known bicyclo[3.3.1]non-2-ene-7-carboxylic acid (7)[8] and 1-noradamantanecarboxylic acid (8)[9], respectively. Other ketones were recovered unreacted under the same condition. Inertness of the stereoisomer 5, making a strong contrast to the ready conversion of 2 to 7, may indicates a stereoelectronic control of the present conversion as shown in 6.

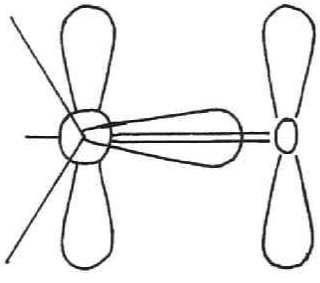


2 6 7



4 8

In Table II are summarized the relative amounts of the five monobromoadamantanones, which were ascertained to correspond to the kinetically controlled product distributions. As shown in Table II, the reaction took place preferentially at the C_γ position. An important finding was that the other bridgehead position, C_α, α to the carbonyl, had considerably reduced reactivity toward hydrogen abstraction in strong contrast to a nonrigid aliphatic ketone which usually gave the α-bromo ketone under similar condition.[4] The deactivation is presumably due to the rigid bridgehead structure, which prevents resonance stabilization[10] by fixing the carbonyl π orbital perpendicular to the orbital of the odd electron, leaving only the operation of the inductive effect of the carbonyl.



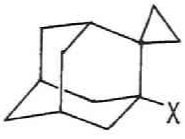
The geometrical inhibition of resonance stabilization by an adjacent (pseudo) π system, as elusidated directly in the depressed (compared

Table II. Product Ratio and Reactivity Ratio of Bromination of Adamantanone

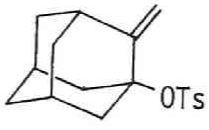
Reagent	Solvent	Product ratio[a]					Reactivity ratio	
		1	2	3	4	5[b]	C_γ to C_α	C_β to C_δ[e]
$BrCCl_3$[c]	$BrCCl_3$	9.8	4.3	1.7	1.1	1.0	9.0	0.78
NBS	C_6H_5Cl	5.0	2.4	0.47	0.75	1.0	6.7	1.8
CH_2Br_2[d]	CH_2Br_2	5.3	2.3	0.72	0.67	1.0	7.9	1.2

(a) Determination was made by glpc peak area method and the values listed are averages of more than one run. (b) Taken as a standard. (c) Ther were some unidentified byproducts (presumably chloroadamantanones by glpc analysis, although their identification was not complete), the total amount of which was about 3 % of the total amount of the brominated products. Reinvestigation revealed that the reaction of adamantane with bromotrichloromethane gave bromoadamantane together with a small amount (ca. 5 %) of 1-chloroadamantane. (d) In the case of dibromomethane, the chain length was short, so that prolonged reaction time with a large amount of initiator was necessary. (e) The product ratio of the β-substituted isomers 2 and 5 to the δ-substituted isomer 3 was converted to the statistically corrected reactivity ratio.

with unsubstituted model compounds) solvolysis rates of spiro-[cyclopropane-1,2'-adamantyl] chloride[10a] or tosylate[10b] (9) and 2-methyleneadamantyl tosylate[10b] (10), thus became evident also in the case of free radicals.



9 X=Cl, OTs

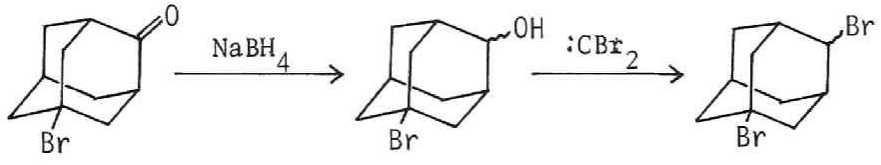


10

As for the radical chain transfer step, the equatorial attack (equatorial to the cyclohexane ring containing the carbonyl, leading to 2) to the C_β radical of adamantanone was found to be preferential to the axial attack (leading to 5). A similar stereoselective radical substitution at the homoallylic position has also been observed in the case of 7-norbornenyl radical.[11] In substituted cyclohexyl radicals, the atom transfer takes place preferentially from the trans direction to the electronegative substituent.[12] Such a phenomenon, called as trans effect, has been interpreted in terms of the electronic dipolar interaction.[12] The present stereoselective equatorial substitution may also be the result of such a dipolar effect. However, the dependence of stereoselectivity on the brominating reagent (Table II), coupled with the published result[13] that the Hunsdiecker reaction of 4(e)-carboxyadamantan-2-one afforded

2 and 5 in a ratio of 1.7:1,[13] may show that a steric factor is, in part, responsible for the stereoselectivity.

The predominant formation and ready chromatographic separation of bromo ketone 1 may be a major synthetic merit of the present bromination of adamantanone. The sodium borohydride reduction of 1 resulted in the formation of 1-bromoadamantan-4-ol (11), which, in turn, gave 1,4-dibromoadamantane (12) by the dibromocarbene bromination.



1 11 12

Further, the ready conversion of bromo ketone 2 to bicyclo-[3.3.1]non-2-ene-7-carboxylic acid may promise a convenient preparation of bicyclo[3.3.1]non-2-ene derivatives.

2.4 Experimental

Materials

Commercially available adamantanone (ldrich) was used as a substrate. NBS was prepared by a standard procedure. Bromotrichloromethane, dibromomethane, and chlorobenzene were shaken with concentrated sulfuric acid until the acid layer became colorless and distilled over phosphorous pentoxide.[14]

Bromination of Adamantanone

A mixture of 1 g of adamantanone, 2 g of NBS, 0.5 g of DTBP in 20 ml of chlorobenzene was heated at 100-110° under nitrogen. Occasionally the mixture was analyzed by glpc and additional NBS and DTBP were added until the conversion reached to 30-50%. At the end of the reaction 20 ml of water was added and the mixture was extracted with four portions of 30 ml of ether. The combined ether extract was washed with dilute aqueous sodium hydroxide and then with water, dried on sodium sulfate and concentrated to dryness. The residue was sublimed at a reduced pressure and a silica gel column chromatography was made on the sublimate to allow rough separation of the bromoadamantanones. Every pure bromo ketone was obtained by means of preparative glpc separation followed by repeated recrystallization from hexane. More conveniently bromo ketones 1, 3, and 5 were separated after bromo ketones 2 and 4 had been converted to bicyclo[3.3.1]non-2-ene-7-carboxylic acid (7) and 1-noradamantane-carboxylic acid (8), respectively, under the Favorskii condition. Melting points, carbonyl sytetching frequencies, uv, and nmr spectra of bromoadamantanones were shown in Table I, Figure 2.

1-Bromoadamantan-2-one (4)

The authentic 1-bromoadamantan-2-one was prepared by the Hunsdiecker reaction of 1-carboxyadamantan-2-one.[6] The experimental details will be given in Chapter 3.

Favorskii Rearrangement

The procedure of the double Favorskii rearrangement of 1,3-dibromoadamantane-4,8-dione[15] was applied to the bromo ketone mixture. Thus, a solution of 1.8 g of a bromination mixture of adamantanone (containing a large amount of unreacted adamantanone) and 2 g of potassium hydroxide in 10 ml of ethanol and 7 ml of water was refluxed for 2 hr. About half of ethanol was distilled off in vacuo and 20 ml of ether was added. The mixture was extracted with four portions of 10 ml of aqueous potassium hydroxide. The aqueous layer was washed with ether. The ether layer and the ether washing were combined and dried over sodium sulfate. Evaporation of the ether gave 1 g of a mixture of bromo ketones 1, 3, and 5 in a ratio similar to the original one. The aqueous layer was acidified with hydrochloric acid and extracted with three portions of 30 ml of chloroform. The chloroform was evaporated in vacuo and the residue was esterified with diazomethane. Distillation at 50-82°/3 mmHg afforded 0.2 g of an oil which was approximately a 1:4 mixture of methyl 1-noradamantanecarboxylate (13) and methyl bicyclo[3.3.1]non-2-ene-7-carboxylate (14). 14 was obtained by a preparative glpc separation; ir(neat) 1725 cm^{-1}; nmr ($CDCl_3$, TMS) τ 4.37 (2H, broad s, olefinic), 6.37 (1H, s, methyl), and 7.25-8.55 (11H, complex m, methlene and methine). 13 was also isolated by a preparative glpc separation after 14 had been converted to the addition compound with bromine; ir(neat) 1730 cm^{-1}; mass spectral molecular peak at m/e 180.

1-Bromoadamantan-4-ol (11) and 1,4-Dibromoadamantane (12)

A mixture of 330 mg of 1-bromoadamantan-4-one (1) and 50 mg of sodium borohydride in 5 ml of DMF was stirred for 20 hr. Most of the DMF was distilled in vacuo. Water was added and the mixture was extracted with three portions of 15 ml of ether. The combined ether extract was washed with water and dried over sodium sulfate. Evaporation of ether gave 314 mg (95%) of 1-bromoadamantan-4-ol (11), which was recrystallized from cyclohexane ; ir (KBr) 1107, 1090, 1055, 1010, 815, and 800 cm^{-1} ; nmr (CCl_4, TMS) τ 6.13 and 6.27 (1H, broad s, CHOH) and 7.30-8.80 (14H, m with peaks at 7.47, 7.70, 7.98, 8.26, 8.47, and 8.70, remaining adamantyl and hydroxyl protons). No further purification was attempted on this oxybromide. To a vigorously stirred mixture of 154 mg of 11 (ca. 1:1 mixture of stereoisomers), 2 ml of 50% aqueous sodium hydroxide, and 0.2 ml of benzene emulsified by 30 mg of triethylbenzylammonium chloride was added dropwise 3 ml of bromoform in a period of 2 hr. After stirring for 6 hr, 30 ml of water was added and the mixture was extracted with ether. The solvent was expelled and the residue was chromatographed on a silica gel column. Elution with n-hexane gave 60 mg (30%) of 12 as a 1:1 mixture of stereoisomers ; ir (KBr) 1023, 940, 920, 817, 807, and 744 cm^{-1} ; nmr (CCl_4, TMS) τ 5.53 (1H, broad s, CHBr) and 6.90-8.20 (13H, m with peaks at 6.96, 7.13, 7.70, 7.92, and 8.05, remaining protons).

Anal. Calcd for $C_{10}H_{14}Br_2$: C, 40.85; H, 4.80.

Found : C, 41.00; H, 5.11

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Chapter 3

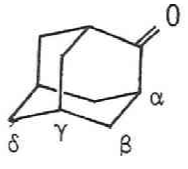
α-Bromoadamantanone

3.1 Summary

α-Bromoadamantanone has been prepared by the Cristol modified Hunsdiecker reaction of α-carboxyadamantanone obtained from adamantane via six steps.

3.2 Introduction

Using adamantane as a model substrate, the reactivity problem such as the substituent effects of aliphatic compounds have been treated quantitatively in recent years.[1] The most noteworthy point in the preliminary studies on bromination (both ionic[2] and free radical[3]) of adamantanone was that no activation of the α position



to the carbonyl was observed. Prolonged heation of adamantanone in dry bromine in the presence of aluminum bromide gave γ-bromo-adamantanone along with a small amount of the δ isomer.[2] Serious deactivation of the α position was observed also in the free radical substitutions. The α to γ reactivity ratio was only 0.15 for NBS bromination.[3] In these circumstances, some other procedure should

be employed for the successful preparation of α-bromoadamantanone.

3.3 Results and Discussion

1-Carboxyadamantan-2-one (6), a potential precursor of 1,2-disubstituted adamantanes, was prepared by a modification of the procedure of Peters, et.al.[4] 1-Dichloromethyladamantane (1) obtained by the exclusive bridgehead insertion of dichlorocarbene into adamantane,[5] was converted in a yield of 63% to homoadamantan-4-one (2) via hydrolytic rearrangement in hot phosphoric acid.[5] Oxidation of 2 with selenium dioxide resulted in the formation of homoadamantane-4,5-dione (3)[6] (56%), which was further oxidized to bicyclo[3.3.1]nonane-3,7-dicarboxylic acid (4) in a yield of 79%. The diacid 4 was, after esterification with diazomethane, recyclized to 1-carbomethoxyadamantan-2-one (75%), which was readily converted to the keto acid (6)[4] on hydrolysis (80%).

The Cristol modified Hunsdiecker reaction was carried out on the keto acid 6 in ethylene bromide. The reaction proceeded with an appreciable rate and gave the desired product, α-bromoadamantanone (8) in a good yield (71%), indicating that the Hunsdiecker reaction readily proceeded in the presence of α-carbonyl group and that the resultant α-bromoadamantanone (8) was stable under the condition employed.*) In light of the generally accepted free radical

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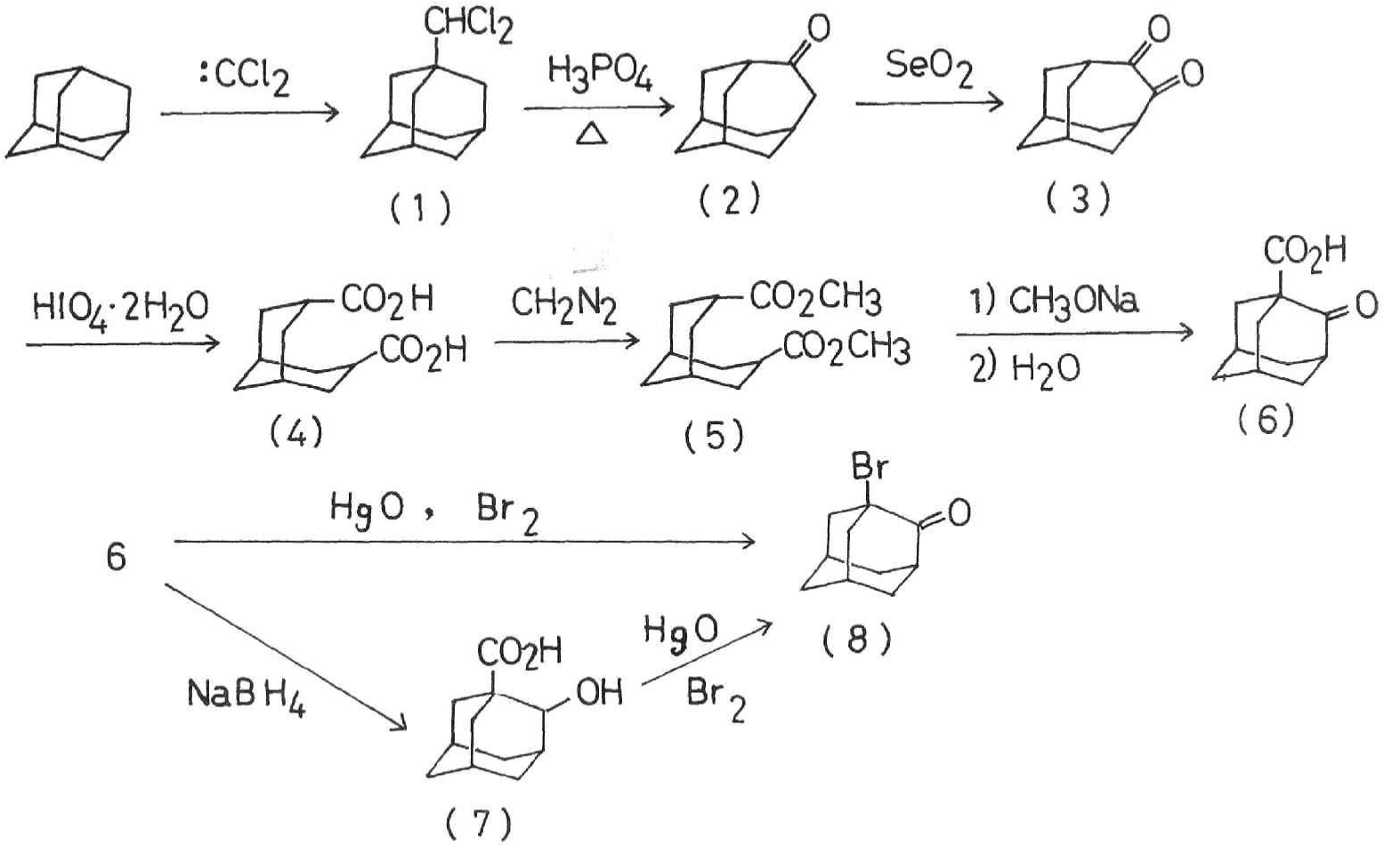
(*) Under basic conditions, α-bromoadamantanone readily undergoes Favorskii rearrangement giving 1-noradamantanecarboxylic acid.[3]


:CCl2
CHCl2
H3PO4
△
O
SeO2
O
O
(1)
(2)
(3)
HIO4·2H2O
CO2H
CO2H
CH2N2
CO2CH3
CO2CH3
1) CH3ONa
2) H2O
CO2H
O
(4)
(5)
(6)
6
HgO , Br2
Br
O
(8)
NaBH4
CO2H
OH
HgO
Br2
(7)

mechanism of the Hunsdiecker reaction, the ready formation of the α-radical of adamantanone by the present procedure is quite interesting when taken in conjunction with the published result of a serious deactivation of the α position of adamantanone toward hydrogen abstraction by an atom or radical.[3)]

Interestingly, under a similar Hunsdiecker condition 1-carboxyadamantan-2-ol (7) obtained by the sodium borohydride reduction of 1-carboxyadamantan-2-one (6) gave also α-bromoadamantanone (8) as a major product.*)

Synthetic merits in the present results lie in the ability of α-bromoadamantanone to give a noradamantane skeleton by the facile Favorskii ring contraction[3)] and in the general applicability of the Hunsdiecker degradation to other polycyclic systems for the successful preparations of 1-bromo-2-oxo derivatives less easily accessible by direct bromination of the parent ketones.

3.4 Experimental

1-Dichloromethyladamantane (1)

To a vigorously stirred mixture of 100 g of adamantane, 1400 ml of 50% (wt/wt) aqueous sodium hydroxide, 140 ml of benzene, and 4 g

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(*) Tungsten lamp photolysis of a carbon tetrachlorode solution of 2-adamantanol containing mercuric oxide and iodine yielded adamantanone in a very low yield (0.2%), the major product being 2-oxaadamantane (54%).[7)]

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of triethylbenzylammonium chloride was added dropwise 500 ml of chloroform during 4 hr with water cooling. The mixture was further stirred at 40° for 5 hr. Ether (500 ml) was added and the mixture was shaken and filtered. The insoluble material was well washed with ether. The filtrate was carefully extracted with five portions of 300 ml of ether. The ether extracts and washings were combined, washed with water, and dried. Evaporation of the ether gave an adamantane-dichloromethyladamantane mixture, which was further subjected to the above described dichlorocarbene insertion until the conversion reached to 60-70%. Unreacted adamantane was carefully removed by sublimation in vacuo and 1-dichloromethyladamantane (1) was obtained (ca. 70 g) by distillation at 102-104°/5 mmHg (lit.[5] 114-115°/8 mmHg).

Homoadamantan-4-one (2)

A mixture of 86 g of 1-dichloromethyladamantane and 1000 ml of 85% phosphoric acid was heated at 120° for 50 hr under a slow flow of nitrogen. Vigorous flow of nitrogen resulted in a low yield of the product. The cooled solution was poured onto ice water and extracted with methylene chlorode. Methylene chloride was evaporated to give 40 g (63%) of homoadamantan-4-one (2).

Homoadamantane-4,5-dione (3)

According to the procedure of Schlatmann,[6] the title compound was prepared by the selenium dioxide oxidation of homoadamantan-4-one (2). Thus, a mixture of 45.5 g of 2, 32 g of selenium dioxide, 140

ml of dioxane, and 6 ml of water was refluxed for 3 hr. The cooled solution was filtered twice. The filtrate was evaporated to give 30 g (56%) of homoadamantane-4,5-dione (3).

Bicyclo[3.3.1]nonane-3,7-dicarboxylic Acid (4)

According to the published method of Peters,[4] a solution of 30 g of homoadamantane-4,5-dione and 80 g of periodic acid in 500 ml of dioxane-130 ml of water was heated at 70° for 70 hr. After the end of the reaction the mixture was filtered. The filtrate was acidified with hydrochloric acid and then extracted with methylene chloride. From the methylene chloride extract was obtained 28 g (79%) of bicyclo[3.3.1]nonane-3,7-dicarboxylic acid (4).

1-Carboxyadamantan-2-one (6)

Bicyclo[3.3.1]nonane-3,7-dicarboxylic acid (4) was esterified with diazomethane in ether. The resulting diester (5); ir 1740 cm^{-1}, nmr τ 6.32 (methyl), was, without attempted purification, subjected to the cyclization. Thus, a solution of 20 g of the diester and 1.2 equivalent of sodium methoxide in 200 ml of methanol was refluxed overnight. About half of the methanol was distilled and 500 ml of saturated aqueous solution of ammonium chloride was added and the mixture was extracted with ether. From the ether extract was obtained 14 g (75%) of 1-carbomethoxyadamantan-2-one; ir 1740 cm^{-1}, nmr τ 6.43 (methyl), which was hydrolyzed in ca. 80% yield in ethanolin potassium hydroxide containing a small amount of water to give 1-carboxyadamantan-2-one (6); ir 1710 cm^{-1} (broad).

1-Carboxyadamantan-2-ol (7)

Experimental details of the preparation of this compound[8] was given in chapter 1.

Hunsdiecker Reaction

To a vigorously stirred mixture of 446 mg of 1-carboxyadamantan-2-one (6) and red mercuric oxide (430 mg) in 10 ml of ethylene bromide was added dropwise 410 mg of bromine in a period of 10 min. The mixture was heated at 70° for half an hour, and then additional bromine (200 mg) was added and the mixture was stirred at room temperature for 6 hr. The inorganic material was removed by filtration and the filtrate was washed with dilute hydrochloric acid, then with water, and dried. Ethylene bromide was removed to give a solid which was chromatographed on a silica gel column. α-Bromoadamantanone (8) (376 mg, 71%) was obtained by elution with benzene. The spectral data of 8 were given in chapter 2. Similarly was carried out the Hunsdiecker reaction of 1-carboxyadamantan-2-ol (7).

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Chapter 4

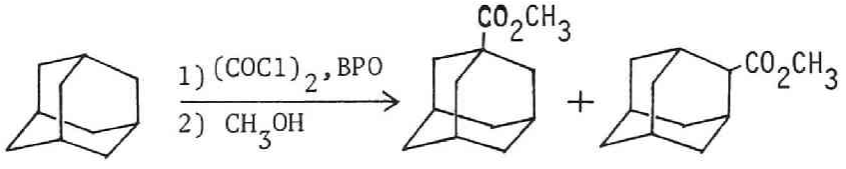
Chlorocarbonylation of Substituted Adamantanes

4.1 Summary

Free radical chlorocarbonylation of 1-methyl, methoxy, carbomethoxy, or cyanoadamantane gave an isomeric mixture of chlorocarbonyladamantanes which were converted to carbomethoxyadamantanes on treatment with methanol. The resulting ester mixture was reduced with lithium aluminum hydride to the methylols which were further converted to the acetates on treatment with acetic anhydride. The bridgehead-to-bridge product ratio of the chlorocarbonylation of each adamantane was determined.

4.2 Introduction

It has been reported by Tabushi, Hamuro, and Oda[1] that the free radical chlorocarbonylation of adamantane afforded a convenient route to 2-adamantanecarboxylic acid, which, otherwise, was accessible only by multistep routes.[2] This novel chlorocarbonylation of adamantane was later applied by Schleyer, et. al. to the synthesis of 2-tert-butyladamantane.[3]



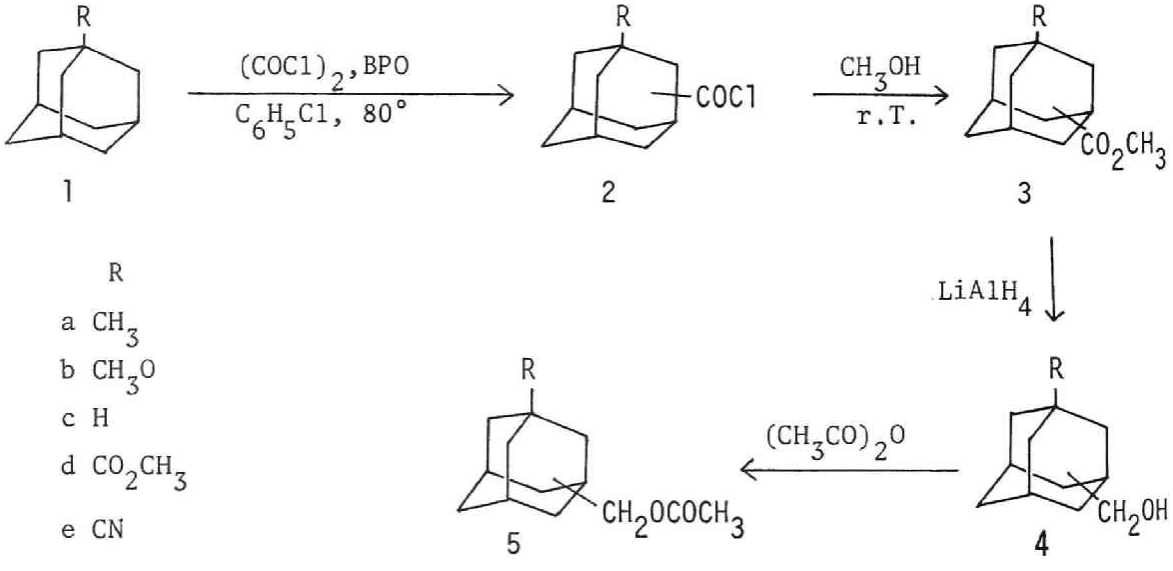
(55%) (45%)

It was further reported that the chlorocarbonylation of norbornane or bicyclo[3.3.0]octane was highly stereoselective.[4)]

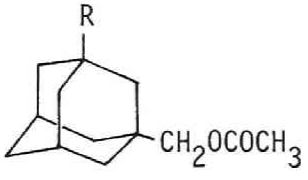
The potential convertibility of a carboxyl function to other functional groups prompted further application of the present chlorocarbonylation also to 1-substituted adamantanes.

4.3 Results and Discussion

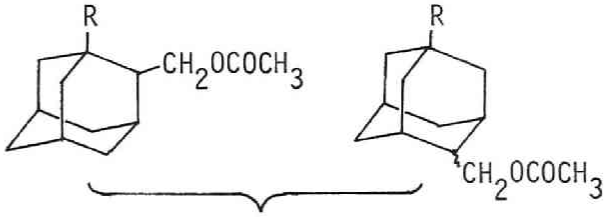
Free radical chlorocarbonylation of 1-methyl, methoxy, carbomethoxy, or cyanoadamantane (1a, 1b, 1d, or 1e) with oxalyl chloride was carried out in chlorobenzene under nitrogen at 80° in the presence of benzoyl peroxide as an initiator. The isomeric mixture of chlorocarbonyladamantanes was , without isolation, converted to a mixture of carbomethoxyadamantanes on treatment with methanol.



Glpc analysis of the ester mixture showed a major peak followed by a set of minor peaks. Without exception, the first eluted, major one was the bridgehead ester. The ester mixture (3) was reduced in practically quantitative yield with lithium aluminum hydride to the carbinols (4) (some minor side reactions were observed for cyano adamantanecarboxylates and adamantanedicarboxylates). The carbinol mixture was further converted to the corresponding acetate mixture (5). Glpc separation was much better for the carbinols (4) or the acetates (5) than for the carboxylates (3). The nmr spectrum of the acetate mixture was especially useful for distinguishing the bridgehead and bridge isomers (5-BH and 5-BR) ; the absorption of the α-methylene protons to oxygen was singlet for 5-BH, whereas doublet for 5-BR.



5-BH



5-BR

Gplc analysis and nmr integration of the carboxylates (3), carbinols (4), and acetates (5) allowed to estimate the ratio of the bridgehead to bridge products. The ratios thus obtained for substituted adamantanes are listed in Table I together with the reported results of halogenation.[5)]

Table I. Apparent Bridgehead-to-Bridge Product Ratio

Substituent	Chloro-carbonylation[a]	Bromination with $BrCCl_3$[b]	Bromination and chlorination with NBS/CCl_4[c]
CH_3	2.3	6.7	2.0
H[d]	1.2	6.1	1.5
OCH_3	5.7	5.7	---
CO_2CH_3	4.4	4.9	2.1
CN	1.4	2.8	0.87

(a) This work; abstracting species: ·Cl

(b) Ref 5a; abstracting species: $\cdot CCl_3$

(c) Ref 5b; abstracting species: $\cdot N(COCH_2)_2$ and/or ·Br

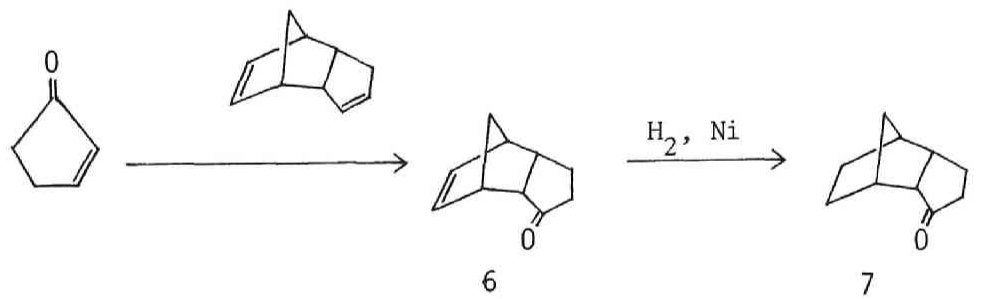
(d) Without statistical correction.

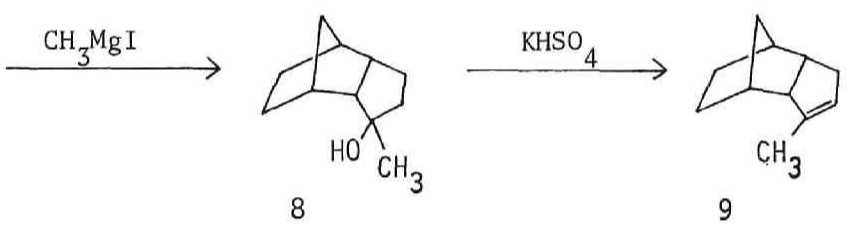
The most interesting observation about chlorocarbonylation of substituted adamantanes was that the apparent substituent effect on the bridgehead-to-bridge product ratios was different from that observed for bromination.[5] The observed bridgehead-to-bridge ratio of bromination with bromotrichloromethane or bromination plus chlorination with N-bromosuccinimide in carbon tetrachloride was in decreasing order with increasing σ^*, while in chlorocarbonylation, the ratio was qualitatively what was expected from steric grounds.

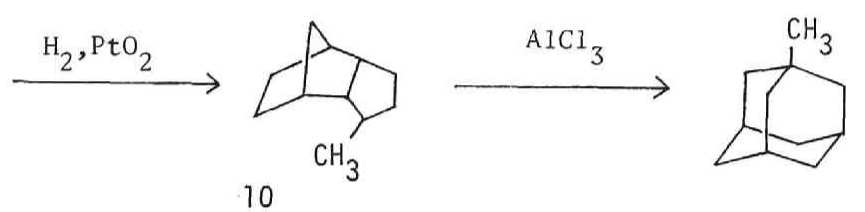
4.4 Experimental

Materials

1-Methyladamantane was prepared by the following sequence.







Thus, a mixture of 93 g of cyclopentenone and 325 g of dicyclopentadiene was heated at 120-130° for 80 hr under stirring. Unreacted cyclopentenone and dicyclopentadiene was removed at 57°/16 mmHg.

The residue was distilled at 67°/3 mmHg to give 90 g of the Diels-Alder adduct 6. To an ether solution of methylmagnesium iodide (prepared from 12 g of magnesium and 80 g of methyl iodide) was added dropwise 50 g of 6 in 100 ml of ether during 1 hr. After the addition was complete the mixture was refluxed for 2 hr, poured onto 1000 ml of ice water. Dilute sulfuric acid was added and the mixture was extracted with ether. Ether was evaporated to give an oil which was distilled at 90-91°/5 mmHg to give 42 g (76%) of the alcohol 7. The alcohol 7 (140 g) was hydrogenated in ethanol in an autoclave using Raney nickel catalyst. The saturated alcohol 8 was obtained by distillation at 73°/3 mmHg. A mixture of 100 g of 8 and 70 g of potassium bisulfate was heated at 110-120° for 23 hr. The mixture was extracted with ether. After drying over sodium sulfate the ether was expelled and 60 g (67%) of the olefin 9 was obtained by distillation at 90-92°/22 mmHg. The olefin 9 (65 g) was hydrogenated using platinum oxide catalyst. Distillation at 86.3-87.3°/19 mmHg afforded 63 g of the hydrocarbon 10. A mixture of 55 g of 10 and 20 g of aluminum chloride was heated at 80-85° under vigorous stirring for 1 hr, then additional 10 g of aluminum chloride was added and the mixture was further stirred for 25 min, carefully poured onto ice, and extracted with ether. The ether extract was dried over sodium sulfate and ether was distilled. About 30 g (56%) of crude 1-methyladamantane (1a) was obtained by distillation at 85-87°/28 mmHg, which was recrystallized from ethanol at a dry ice-aceton temperature.

Further distillation at 100-160°/3-8 mmHg afforded 10 g of an oil, the structure of which was not investigated.

1-Methoxyadamantane was prepared by the silver assisted displacement of 1-bromoadamantane in methanol.[5a)]

1-Carbomethoxyadamantane was obtained by the Fischer esterification of the acid which was prepared by a Koch-Haaf carboxylation of adamantane.[6)]

1-Cyanoadamantane was prepared from 1-bromoadamantane and cupric cyanide in pyridine.[5a)]

General Procedure of Chlorocarbonylation of Substituted Adamantanes

Chlorobenzene solution of oxalyl chloride (n/2 mole) and benzoyl peroxide (n/10 mole) was added dropwise into a solution of a 1-substituted adamantane (n mole) and oxalyl chloride (n/2 mole) in chlorobenzene at 80° under nitrogen. After stirring at 80° for 24 hr, a large excess amount of methanol was added into the cooled solution. The solution was stirred overnight. The solvent was distilled and the products were separated from the starting material either by distillation or column chromatography. The esters obtained were converted to the methylols with lithium aluminum hydride in ether. The methylols were further converted to the acetates in acetic anhydride.

Chlorocarbonylation of 1-Methyladamantane (1a)

According to the general procedure described above, an isomeric mixture of methyl 1-methyadamantanecarboxylates (3a) was obtained

by distillation at 102-104°/6 mmHg, ir 1735 cm^{-1} (52% preparative yield based on methyladamantane used and 93% based on the hydrocarbon consumed). Methylols (4) boiled at 85-110°/6 mmHg. The acetate mixture (5a) showed in its nmr spectrum the absorption of α-methylene protons to oxygen; singlet at τ 6.38 and a set of doublets at τ 5.96, 5.89, and 5.78 (J's were practically the same, being ca. 7 Hz) (CCl_4, TMS). From the integration of these peaks was calculated the bridgehead-to-bridge ratio of 2.3:1.

Chlorocarbonylation of 1-Methoxyadamantane (1b)

Carboxylates (3b) boiled at 103-110°/2 mmHg, ir 1735 cm^{-1}. Methylols (4b) boiled at 83-115°/3 mmHg. Acetates (5b) boiled at 108-118°/7 mmHg. The nmr spectrum (CCl_4, TMS) of 5b showed a singlet at τ 6.84 and three doublets at τ 5.97, 5.92, and 5.89. The product ratio of 5.7:1 was calculated from integration.

Chlorocarbonylation of 1-Carbomethoxyadamantane (1d)

Dicarboxylates (3d) boiled at 74-128°/0.6 mmHg. Diacetates (5d) boiled at 127°/0.3-0.5 mmHg. Some minor side reactions (which were not further investigated) were observed in the course of the acetylation of the methylols (4d). The product ratio of 4.4:1 was obtained from a glpc analysis of the dicarboxylates (3d) using a poly (ethylene glycol) column.

Chlorocarbonylation of 1-Cyanoadamantane (1e)

The carboxylates (3e) were separated from the starting material 1e

by means of column chromatography on silica gel using ethyl acetate-petroleum ether (1:4) as an eluent. The carboxylate mixture (3e) showed absorption at 2260 and 1735 cm^{-1} in its ir spectrum. The product ratio was calculated from a gas chromatogram of the carboxylates (3e).

Preparation of Authentic Samples

Authentic methyl 3-methyladamantane-1-carboxylate, 3-methyl-adamantyl-1-methanol were prepared from relevantly synthesized 3-methyladamantane-1-carboxylic acid.[7] Similarly were prepared: methyl3-methoxyadamantane-1-carboxylate and 3-methoxyadamantyl-1-methanol from known 3-methoxyadamantane-1-carboxylic acid,[8] dimethyl adamantane-1,3-dicarboxylate and 1,3-dihydroxymethyladamantane from adamantane-1,3-dicarboxylic acid.[8]

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Chapter 5

Dichloromethyldiamantanes, Homodiamantanones, and Homodiamantane

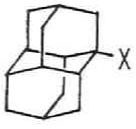
5.1 Summary

The reaction of diamantane (1a) with dichlorocarbene generated from chloroform in an alkaline emulsion gave, in a practically quantitative yield, 1- and 4-dichloromethyldiamantanes (2) and (3) in a ratio of 1.7:1. The 4 position was thus found to be more reactive than the 1 position by a factor of 1.8 if the statistical correction was made. On treatment with hot phophoric acid at 160° 2 only gave diamantane and 1-diamantanecarboxaldehyde (9), whereas under similar conditions 3 gave homodiamantanone (7) along with diamantane and 4-diamantanecarboxaldehyde (10). Diazomethane ring homologation of diamantanone (11) was also useful to prepare homodiamantanones (6) and (7), which were readily reduced to homodiamantane (12).

5.2 Introduction

The pentacyclic hydrocarbon diamantane[1,2] (1a, formally called as congressane) offers interesting investigations on bridgehead reactivities. There are two different kinds of bridgehead positions in 1a, i.e., 1 (conventionally called as "belt") and 4 ("apical") positions.[2] Ionic bromination of 1a gives 1-bromodiamantane (1b) preferentially under condition where adamantane does not undergo

bromination appreciably.[2,3] The enhanced reactivity of the 1

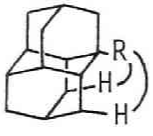


1 a X=H

b X=Br

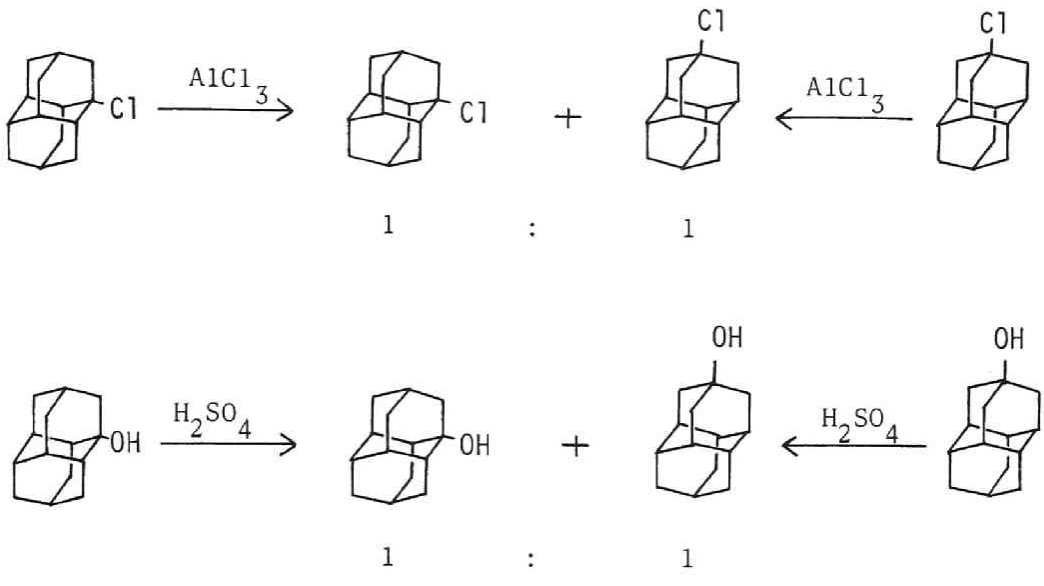
position may possibly the result of slight flattening of this bridgehead in the ground state[4] and/or an inductive effect.

In principle, because of their equatorial character, 4-substituted diamantanes should be the most stable thermodynamically. 1-Derivatives are axial to one cyclohexane ring and suffer from 1,3 nonbonded interactions as indicated. Thermodynamically controlled

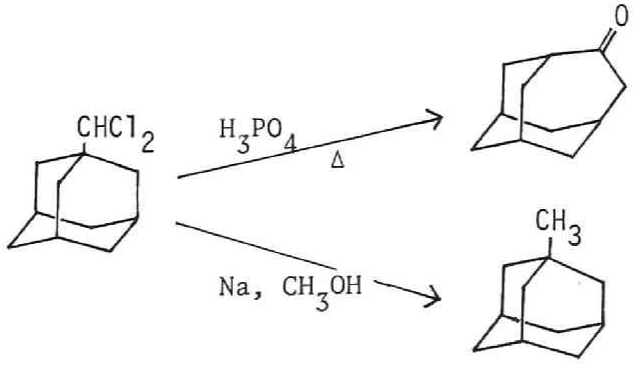


reactions should thus give 4-derivatives. This expectation have been realized in some cases. Aluminum chloride catalyzed rearrangement of exo-tetrahydrotricyclopentadiene gave 4-methyldiamantane (5).[3] Thermodynamic equilibration of chloro or hydroxydiamantane afforded a 1:1 mixture of 1- and 4-derivatives.

The dichlorocarbene insertion, already applied to adamantane,[6] may be another approach to the kinetically controlled attack at the

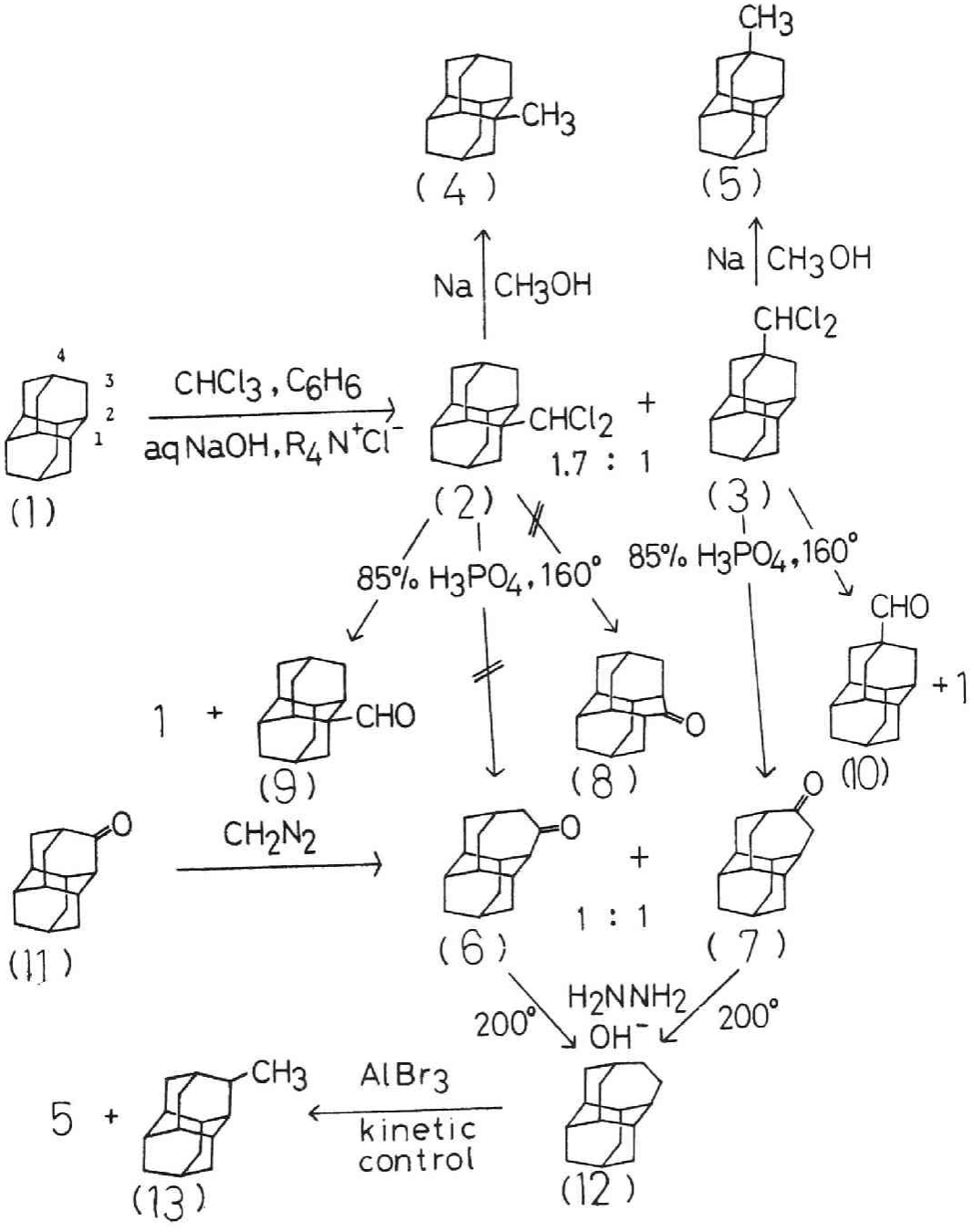


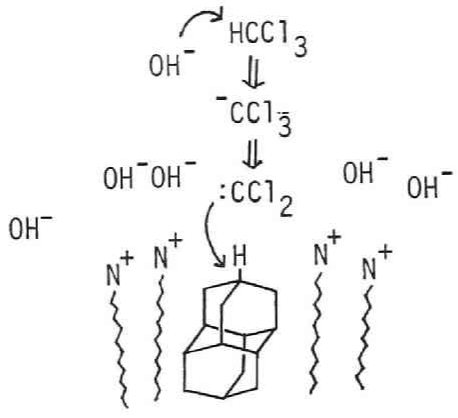
less hindered 4 position. The product, dichloromethyldiamantane, may be an interesting synthetic intermediate from its analogy with dichloromethyladamantane[6], which readily gives homoadamantanone[6] (via hydrolytic rearrangement in 85% phosphoric acid) and methyladamantane (via reduction with sodium in methanol).



5.3 Results and Discussion

The reaction of diamantane (1a) with dichlorocarbene from chloroform in an alkaline emulsion[6] gave, in practically quantitative yield, the bridgehead inserted product, which consisted of 1- and 4-dichloromethyldiamantanes (2) and (3) in a 1.7:1 ratio. As with adamantane,[6] no significant attack at the bridge positions was observed. The major isomer (2) was readily isolated by repeated recrystallization from pentane, while the minor isomer (3) was difficult to be purified in a preparative scale and was obtained by means of a preparative glpc separation. The structures of 2 and 3 were proved by their nearly quantitative conversions to the corresponding 1- and 4-methyldiamantanes (4[7,8] and 5[3,8]) by reduction with sodium in methanol. The observed ratio (1.7:1) of 1- to 4 insertion indicates that the 4 position is more reactive than the 1 position by a factor of 1.8 if the statistical correction is made for the number of hydrogens. Thus, the kinetic preference of the 1 position to 4 position has been realized, for the first time, in the present dichlorocarbene insertion. The results are even surprising when it is taken into account that the 1 position is far more reactive than the 4 position in commom ionic electrophilic substitutions and that dichlorocarbene generated by our procedure is electrophilic.[9] The higher reactivity of the 4 position (than the 1 position) toward dichlorocarbene insertion might be related with the microstructure of the emulsion, although further explanation seems to be requested.


CH3
(4)
(5)
Na | CH3OH
Na | CH3OH
CHCl2
4
3
2
1
CHCl3, C6H6
aq NaOH, R4N+Cl-
CHCl2
+
1.7 : 1
(1)
(2)
(3)
85% H3PO4, 160°
85% H3PO4, 160°
CHO
1 +
CHO
+1
(9)
(8)
(10)
O
O
CH2N2
+
1 : 1
(11)
(6)
(7)
200°
H2NNH2
OH-
200°
5 +
CH3
AlBr3
kinetic
control
(13)
(12)



Interestingly, treatment of 2 and 3 under conditions where adamantane would give homoadamantanone did not give rise either to homodiamantanones 6 and 7 or to isohomodiamantanone (8) ; both 2 and 3 were unreactive. Under more vigorous conditions (160°, 85% phosphoric acid in a sealed tube) 2 gave only diamantane and a small amount of 1-diamantanecarboxaldehyde (9) in 65% combined yield. However the ratio of diamantane to diamantanecarboxaldehyde was not perfectly reproducible. A plausible mechanism for diamantane formation is decarbonylation of diamantanecarboxaldehyde, which may be catalyzed by a trace of oxygen or some other unknown materials. Failure in the expected formation of homodiamantanone may be due to increase in strain upon ring homologation. On the other hand, under similar conditions a 1:1 mixture of 2 and 3 gave homodiamantanone 7 in 20% yield, together with diamantane (30-40%), diamantanecarboxaldehydes 9 and 10 (10-20%), and a small amount of acidic material.

Diazomethane ring homologation of diamantanone (11)[2] affords a convenient alternative route to homodiamantanone system, a 1:1 mixture

of two homodiamantanone isomers 6 and 7 being obtained in 96% yield.* The isomer of lower retention time (carbowax) was identical to 7, obtained unambiguously by rearrangement of 3. The other homodiamantanone was assigned structure 6. The mixture of homodiamantanones 6 and 7 was reduced to homodiamantane (12), mp 136.2-137.4°, in 88% yield.* Treatment of homodiamantane with aluminum bromide leaded to the formation of methyldiamantanes.* Interestingly, the least stable 3-methyl isomer (13)[2,8] predominated at short reaction times (0° and 25°); 4-methyldiamantane (5) was also formed, but none of the 1-isomer.* At higher temperatures and longer reaction times, the equilibrium[2,7] composition containing more than 95% 5 was achieved.*

5.4 Experimental

Dichlorocarbene Insertion into Diamantane

To a vigorously stirred mixture of 1 g of diamantane, 2.5 ml of benzene, and 25 ml of 50% (wt/wt) aqueous sodium hydroxide emulsified by 120 ml of triethylbenzylammonium chloride was added dropwise 10 ml of chloroform in a period of 2 hr. The mixture was further stirred at 40-45° for 10 hr, poured on water and extracted with ether or chloroform. The extract was washed with water and dried over sodium sulfate. The above described procedure was repeated until the

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(*) Experiments were carried out at Princeton University

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conversion of diamantane to dichloromethyldiamantanes (2) and (3) to 80-90%. Finally the solvent was expelled to give 1.5 g of a mixture of 2 and 3 (in a ratio of 1.7:1) which was repeatedly recrystallized from pentane or methanol to give 0.4 g of pure 2; mp 110.5-112°, ir (KBr) 731 cm^{-1}, nmr (CCl_4, TMS) τ 4.55 (1H, s, $CHCl_2$). The mother liquid contained 2 and 3 in a 1:1 ratio. Pure 3 was obtained by means of preparative glpc separation; mp 70°, nmr (CCl_4, TMS) τ 4.45 (1H, s, $C\underline{H}Cl_2$).

Reduction of Dichloromethyldiamantanes

To a vigorously stirred solution of 0.1 g of a mixture of 2 and 3 in 3 ml of methanol was added in small portions 0.5 g of sodium. Then additional methanol (2 ml) was added and the mixture was refluxed for 2 hr. Water (10 ml) was added and the mixture was extracted with three portions of 10 ml of pentane. Pentane was distilled off and the residue (mixture of methyldiamantane and dichloromethyldiamantane) was again treated similarly as described above to complete the conversion. Identification of the products, 1- and 4-methyldiamantane (4) and (5) was made on the basis of their identical retention times with those of authentic 4[7,8] and 5[2,8]. The nmr spectrum showed two methyl signals at τ 9.08 (for 2) and 9.20 (for 3) in a ratio of 1.7:1.

1-Dichloromethyldiamantane in Hot Phosphoric Acid

A mixture of 150 mg of 1-dichloromethyldiamantane (2) and 15 ml of 85% phosphoric acid was sealed and heated at 160° for 20 hr. Water (50 ml) was added and the mixture was extracted with three

portions of 15 ml of methylene chloride. The methylene chloride extract was washed with water and dried. Evaporation of the methylene chloride gave a yellow to brown solid which was chromatographed on a silica gel column. Elution with hexane gave 40 mg (38%) of diamantane. Further elution with hexane-methylene chloride (3:1) gave 32 mg (27%) of 1-diamantanecarboxaldehyde (9); ir (KBr) 1730 cm^{-1}, nmr (CCl_4, TMS) τ 0.70 (1H, s, CHO).

Dichloromethydiamantanes 2 and 3 in Hot Phosphoric Acid

A 1:1 mixture of 1- and 4-dichloromethyldiamantanes 2 and 3 (120 mg) was subjected to a similar condition as described above and the products were separated by a silica gel column chromatography. Diamantane (25 mg, 30%) was first eluted with hexane. Elution with hexane-methylene chloride (3:1) gave 16 mg of 1- and 4-diamantane-carboxaldehydes 9 and 10. Further elution with hexane-methylene chloride gave 10 mg (20% based on 3) of homodiamantanone 7; mp 168° after two recrystallization from hexane and methanol; ir $\nu_{C=O}$ 1698 cm^{-1}, nmr (CCl_4, TMS, 100 MHz) τ 7.36 (1H, broad s, bridgehead adjacent to C=O), 2.58 (2H, d, J=4 Hz, methylene adjacent to C=O), and 7.9-8.4 (17H, broad, others); mass spectral molecular peak at m/e 2.6.

4.5 References

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(c) T. M. Gund, V. Z. Williams, Jr., E. Osawa, and P. von R. Schleyer, Tetrahedron Lett., 3877 (1970).

(2) T. M. Gund, M. Nomura, V. Z. Williams, Jr., P. von R. Schleyer, Tetrahedron Lett., 4875 (1970).

(3) T. M. Gund and P. von R. Schleyer, ibid., 1583 (1971).

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(7) E. Osawa, Z. Majerski, and P. von R. Schleyer, J. Org. Chem., 36, 205 (1971).

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(9) I. Tabushi, Z. Yoshida, and N. Takahashi, presemted at the 11th Symposium on Organic Radical Reactions, Tokyo, 1970, Abstracts, p 28....

Part 2

Some Mechanistic Aspects in Aliphatic Free Radical Reactions

Chapter 6

Abnormal Benzo Substituent Effect on Free Radical Formation Process. A Local Symmetry Effect.

6.1 Summary

Relative stabilities of 1-bicyclo[2.2.2]octyl (9), 1-benzobicyclo-[2.2.2]octenyl (10), 1-dibenzobicyclo[2.2.2]octadienyl (11), and 1-tribenzobicyclo[2.2.2]octatrienyl (12) radicals were obtained by relative rates of the free radical bromine abstraction from the corresponding bridgehead bromides by a silyl radical. It was found that 9 and 12 were appreciably more stable than expected. The observed order of stability 9>10>12>11 can not be explained by the well established concepts alone. The extra stabilization of 9 or 12 (or destabilization of 10 or 11) was interpreted in terms of the local symmetry (or local asymmetry) of these radicals.

6.2 Introduction

In the course of investigations on factors which influence the radical stability, the stability of a strained radical has received much attention in connection with the stable conformation of a free radical.[1] A preferred planar or nearly planar geometry of a simple, unrestricted alkyl radical has been a generally accepted hypothesis from vacuum ultraviolet[2] and electron spin resonance[3] spectroscopies, formation of a racemized product from an optically active substrate,[4]

and theoretical calculations.[5] The direct kinetic investigation of decomposition of a series of bridgehead peresters[6] (or azo derivatives[7]) having different bridgehead planarities such as adamantyl, bicyclo[2.2.2]octyl, and bicyclo[2.2.1]heptyl has shown that the decomposition rates were in fact depressed, but not so dramatically as in solvolysis reactions, with increasing bridgehead nonplanarity. The instability of a strained bridgehead radical was further demonstrated by decarbonylation of a similar series of bridgehead aldehydes[8] and also by unsuccessful bridgehead hydrogen abstraction from strained bicyclo[2.2.1]heptane[9] or bicyclo[2.1.1]hexane[10] in contrast to the ready abstraction of the bridgehead hydrogen of less strained adamantane[11] or bicyclo[2.2.2]octane.[12] All of the results cited above seem to suggest that strain, especially angle strain may be the determining factor of the bridgehead radical stability. It has also been reported that the relative rates of hydrogen abstraction from a series of aliphatic polycyclic hydrocarbons by the trichloromethyl radical were correlated with a computer analysis of the change in strain energy in going from the ground state to the radical.[13] In this respect a curious observation was reported by Wiberg and coworkers, who were able to show the synthetic utility of the free radical bridgehead substitution on bicyclo[1.1.1]pentane via the bicyclo[1.1.1]pentyl radical which had the greatest deviation from planarity ever known.[14]

For these highly strained substrates where no direct kinetic data

are available, the bridgehead-to-bridge reactivity ratio in the free radical substitutions (halogenation, chlorocarbonylation, etc.) on the parent hydrocarbons (Table I) may be an alternative measure of the bridgehead radical stability, for, as illustrated in the relative reactivities of some polycyclic hydrocarbons toward autoxidation,[15] the bridgehead reactivities are generally more sensitive to a structural change than the bridge reactivities presumably because of ease with which the bridge radical (compared with the bridgehead) takes planarity or near planarity. The variation in the ratios of the bridgehead-to-bridge reactivity listed in Table I is not fully understood from consideration of the bridgehead angle strain alone but interpreted by taking the geometrical symmetry of the bridgehead also into consideration. In fact, among the compounds in Table I only those which yield symmetrical radicals such as adamantane, bicyclo---[2.2.2]octane, and bicyclo[1.1.1]pentane or those which yield radicals of similar symmetry only with respect to the vicinal carbons (it may be called as "local symmetry") such as bicyclo[3.3.0]octane have appreciable bridgehead reactivities. Such may be called a local symmetry effect. An experimental evidence of this hypothesis of a local symmetry effect is presented in this chapter.

6.2 Results

A series of bridgehead bromides (1a, 2a, 3a, and 4a) containing the bicyclo[2.2.2]octane framework was prepared. 1a was prepared by

Table I. Bridgehead-to-Bridge Reactivity Ratios of Some Polycyclic Hydrocarbons in Free Radical Substitutions.[a)]

Substrate	Mode of substitution	Reactivity ratio	Ref
adamantane	chlorination, bromination	3-5	11a
	chlorocarbonylation	3.7	b
bicyclo[2.2.2]octane	chlorination	6.9	12
bicyclo[3.3.0]octane	chlorocarbonylation	2.9	c
bicyclo[2.2.1]heptane	chlorination	0	9
	chlorocarbonylation	0	c
nortricyclane	chlorination	0	d
bicyclo[2.1.1]hexane	chlorination	0	10
tricyclo[3.3.0.$0^{2,6}$]octane	chlorination	0	e
bicyclo[3.1.0]hexane	chlorination	0	f
bicyclo[1.1.1]pentane	chlorination	7	14b
	chlorocarbonylation	17	14b

(a) The ratios are statistically corrected for numbers of hydrogens.

(b) I. Tabushi, J. Hamuro, and R. Oda, J. Org. Chem., 33, 2108 (1968).

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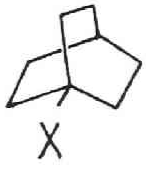
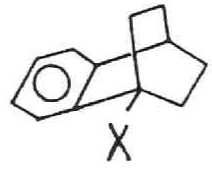
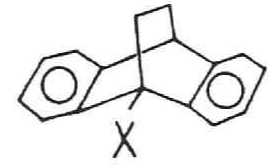


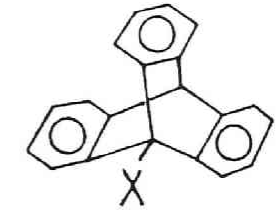
1a X=Br
b X=H
c X=CO_2H



2a X=Br
b X=H
c X=OCH_3
d X=Cl
e X=$OCOCH_3$

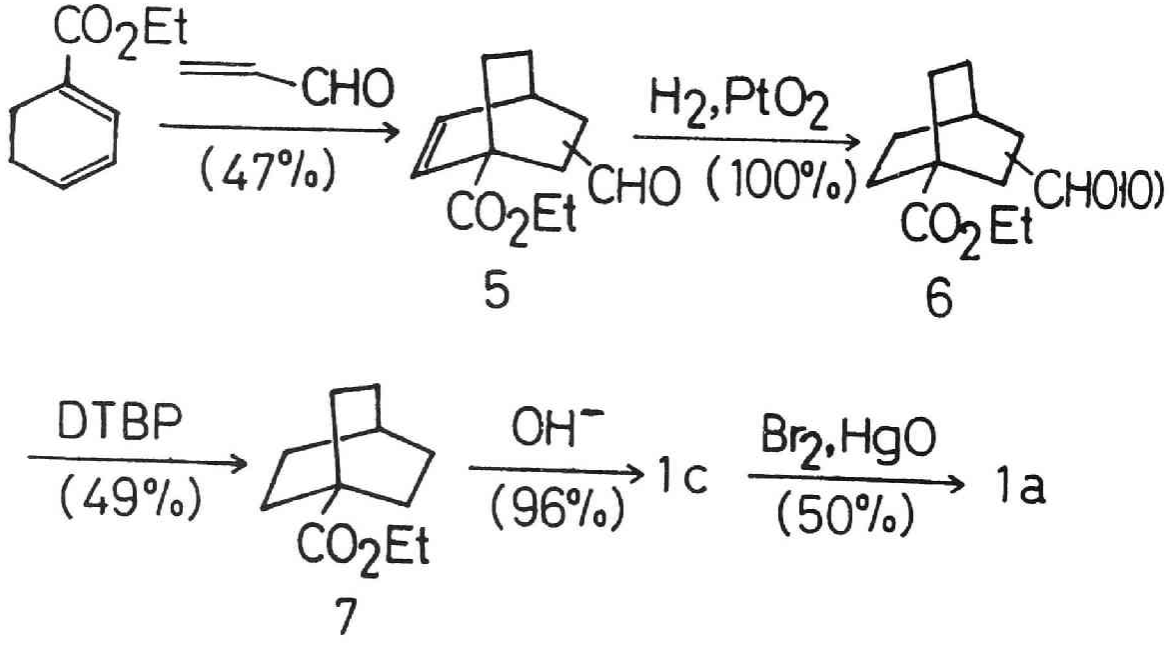


3a X=Br
b X=H

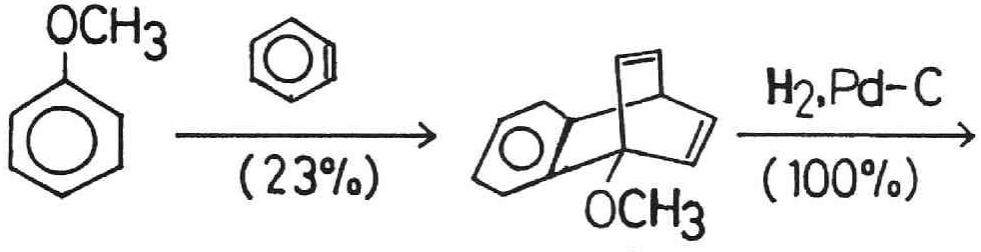


4a X=Br
b X=H

the Hunsdiecker reaction of the corresponding acid (1c)[16] which was obtained by a slight modification of the procedure of Doering.[17]



The procedure of Suzuki and Morita for converting 1-methoxybicyclo[2.2.2]octanes to 1-halobicyclo[2.2.2]octanes[18] was applied to the synthesis of 2a. Thus, the 1,4-adduct of benzyne to anisole was, after hydrogenation, converted to 2a on treatment with acetyl bromide-stannic chloride or stannic bromide.



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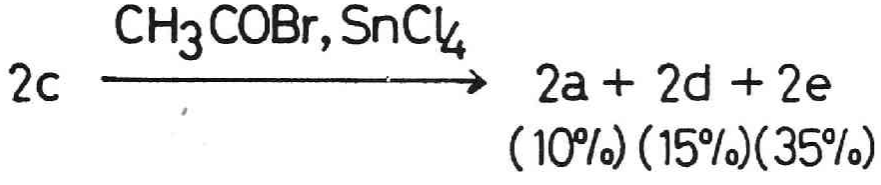


The 1,4-addition of 9-bromoanthracene with ethylene[19] or benzyne[20] gave, in a moderate yield, 3a or 4a, respectively.

The reductive debromination of a bromide (1a, 2a, 3a, or 4a) by methyldichlorosilane was carried out in a degassed, sealed tube in the presence of a catalytic amount of di-tert-butyl peroxide (DTBP) at 120°. The reaction proceeded with an appreciable rate even in the case of 4a. The only detectable product, besides those derived from silanes, was the corresponding hydrocarbon (1b[17], 2b[21], 3b[21], or 4b[20]). That the yield of the reaction was always nearly quantitative indicated that any

side reaction was not appreciable in the present reaction.

To obtain the relative reactivity of a bromide, a competitive reaction was carried out, where a bromide (1a, 2a, or 4a) competed with 3a (standard) for the attack of the silyl radical. Relative reactivities thus obtained were 1a (2.36±0.06), 2a (1.24±0.04). 3a (1, standard), and 4a (1.11±0.04). The logarithms of the relative rates (or the relative free energies of activation) are shown in Figure 1.

6.4 Discussion

Ready Formation of Strained Radicals

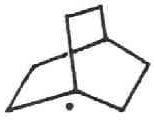
As is well established in many examples[22] the present reductive debromination can be understood in terms of a radical chain mechanism involving the bromine abstraction from 1a, 2a, 3a, or 4a by the methyldichlorosilyl radical followed by the hydrogen transfer to the bridgehead radical thus formed (9, 10, 11, or 12) from the parent hydrosilane.

$$(\underline{\text{tert}}\text{-}C_4H_9O)_2 \longrightarrow \text{tert-}C_4H_9O\cdot$$

$$\underline{\text{tert}}\text{-}C_4H_9O\cdot + HSiCl_2CH_3 \longrightarrow \text{tert-}C_4H_9OH + \cdot SiCl_2CH_3$$

$$\cdot SiCl_2CH_3 + RBr \longrightarrow BrSiCl_2CH_3 + R\cdot$$

$$R\cdot + HSiCl_2CH_3 \longrightarrow RH + \cdot SiCl_2CH_3$$



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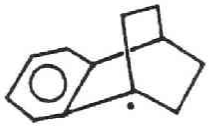

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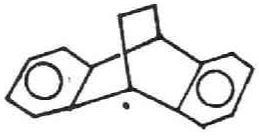

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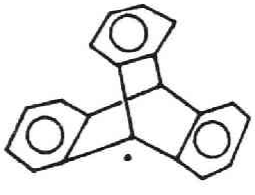

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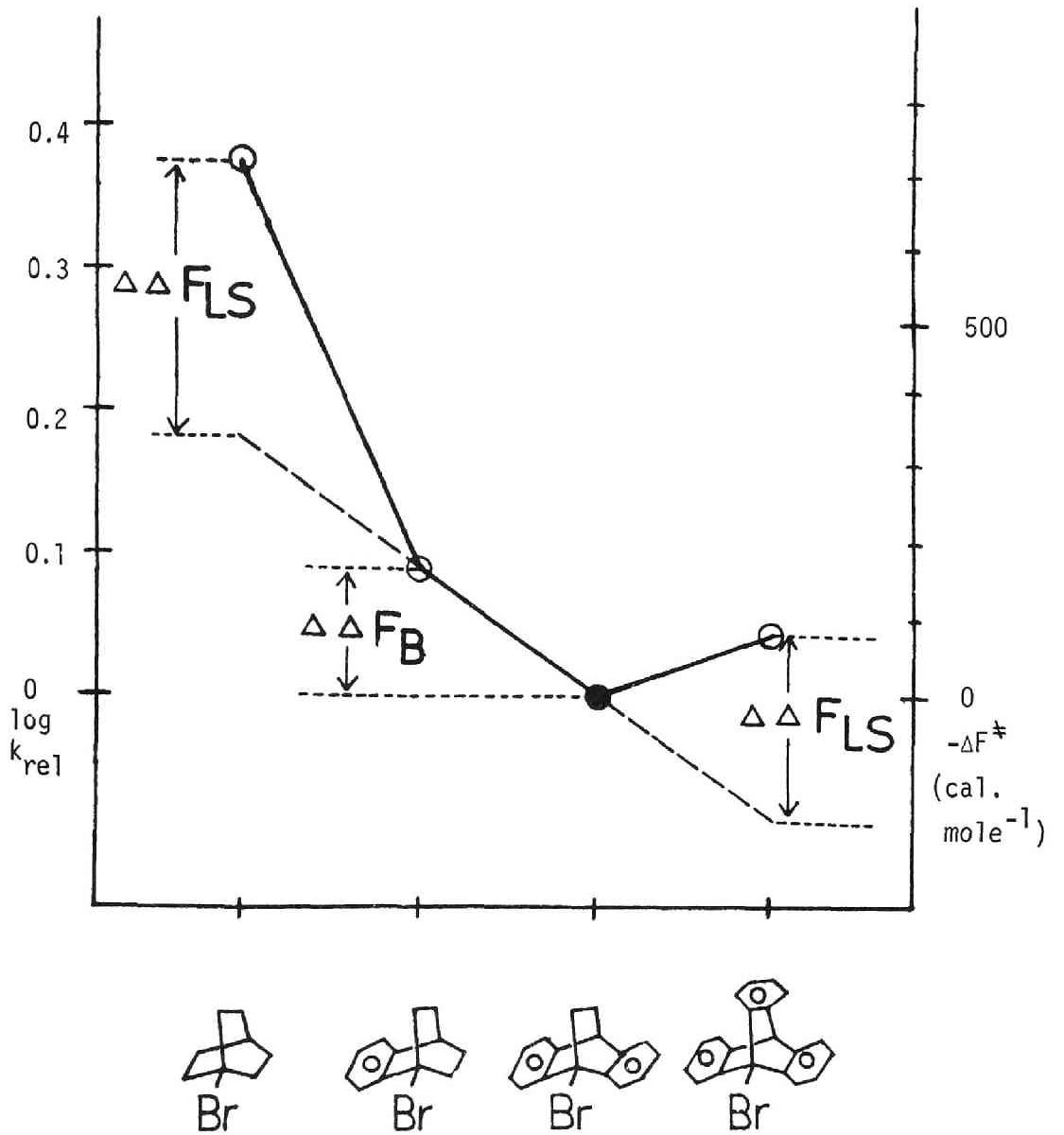

Figure 1. Logarithmic relative rates of the bromine abstraction from 1a, 2a, 3a, and 4a by methyldichlorosilyl radical.

An important and even surprising observation is that the strained radicals 10, 11, or 12 can be generated by the present procedure with a rate not much different from that of 9, although the triptycyl radical (12) is believed to be very unstable in spite of its apparent structural similarity to the stable trityl radical.[23] An attempted formation of 12 via bridgehead hydrogen abstraction of triptycene was unsuccessful.[23a] The instability of 12 was further demonstrated by the observation that 12 generated by thermolysis of triptoyl peroxide readily abstracted hydrogen even from benzene.[23b] The present results show, for the first time, the potentiality of the silyl radical method in ready formation of a strained bridgehead radical which, otherwise, is less accessible, although there is a literature report of a similarly ready formation of the strained 1-norbornyl radical from 1-bromonorbornane via the bromine abstraction by an organotin radical.[24] A significant exothermicity of the bromine abstraction by a silyl radical[25] may be the principal reason for the reduction in the activation energy, which, in turn, necessarily results in a small structural effect on the rate of abstraction. The electroneutral or weakly nucleophilic character of a silyl radical[26] should also be taken into account. The bridgehead carbon is thus nearly electroneutral in the transition state of the bromine abstraction and destabilization may diminish, which originates from steric (strain) or inductive effect on a carbonium ion-like transition state encountered in an usual hydrogen abstraction[27] or a perester decomp-

osition.[28]

Relative Reactivities

The most striking feature of the present results is that the change in the reactivities is not monotonous in going from 1a to 4a (Figure 1). The differences in the reactivities are, although small as mentioned in the previous section, apparent and beyond experimental errors judging from reproducibility of the relative rates and accuracy of the glpc analysis. Although the stepwise introduction of a benzo substituent into the bicyclo[2.2.2]octane framework lowers the reactivity at first, 4a has equal or even greater reactivity than 3a. A benzo substituent would be expected to reduce the bridgehead reactivity because of possible increase in steric crowding around the bridgehead and in the bridgehead strain. On the contrary, an electronegative inductive effect of a benzo substituent may accelerate the reaction by dispersing possible negative charge developing in the transition state owing to the nucleophilic character of a silyl radical,[26] although its nucleophilicity is extremely small. However, an important point is that any (steric, strain, or inductive) effect of successive benzo substitution should be additive, the overall benzo effects should thus be cumulative. If there is no special effect originating from a benzo substituent, the reactivity should monotonously decreased or monotonously increased in going from 1a to 4a, which is not what was observed (Figure 1). Decreasing rates with

increasing benzo substituents show that strain and/or steric decelerating effects surpass the inductive accelerating effect. If the reactivity difference between 2a and 3a, 170 cal.mole^{-1}, is taken as the inherent decelerating benzo effects ($\Delta\Delta F_B$), the present abnormal benzo effects are characterised by the unexpectedly high reactivities of symmetrical 1a and 4a. More properly, asymmetrical 2a or 3a suffers from abnormal destabilizing effect due to its lack of local symmetry. An important conclusion is that some extra stabilization contributes to the radicals 9 and 12 (or destabilization to 10 and 11), which may be correlated with the geometrical symmetry of 9 and 12. The gap between the observed and predicted (from additivity of $\Delta\Delta F_B$, dashed line in Figure 1) reactivities of 1a and 4a ($\Delta\Delta F_{LS}$), some 300 cal.mole^{-1}, is thus ascribed to the local symmetry effect. The introduction of benzo substituent into symmetrical bicyclo[2.2.2]octane is an appreciable perturbation to the geometry (one bond is shortened and thus three C-C-C angles at the bridgehead position become non-equivalent) and the local symmetry effect may disappear (or the local asymmetry destabilization appears). Removal of methylene from bicyclo-[2.2.2]octane to give bicyclo[2.2.1]heptane would be a much great disturbance. The very low reactivity of the bicyclo[2.2.1]heptane bridgehead[9] may, in part, be attributed to the very asymmetrical nature of the 1-bicyclo[2.2.1]heptyl radical, although the main reason is, needless to say, the increase in angle strain of this radical.[13] On the other hand, it is highly plausible that the local symmetry

makes the bicyclo[1.1.1]pentyl[14] or cubyl[29] "stable" fot its appreciable angle strain.

Although the theoretical interpretation of a local symmetry effect has not perfectly been made, the origin of the effect may presumably be related to the mode of the hybridization of a radical in such a way that the hybridization energy is sensitive to the local symmetry. It will be valuable to consider the present effect in light of the nonplanarity of some strained secondary (e.g. cyclopropyl[30]) radicals especially having an electronegative α substituent (e.g. fluorine[31]). The contributing factors to the geometry of a radical may be (1) hybridization energy, (2) repulsion of the bonding electrons (3) nonbonded interactions between the groups at the ends of the bonds. A planar geometry may be preferred from the viewpoint of minimization of repulsions between bonding electrons and between groups. Because the radical is a "middle" between the sp^2 hybridized planar carbonium ion and the sp^3 hybridized tetrahedral carbaniom the hybridization energy of the radical would be less sensitive (than the carbonium ion or carbanion) to planarity.[32] The energy difference between planar and pyramidal structure should be reduced, this is what is usually observed.[6,7,8] An important possibility, then, is that factors other than planarity such as symmetry may contribute significantly to the hybridization energy of the radical of a given structure. At the sacrifice of some unfavorable increase in repulsions between bonds the cyclopropyl radical may prefer a nonplanar geometry because of a

compensating stabilizing hybridization in a pyramidal or more symmetrical structure with respect to the three angles around the radical center. The enhanced configurational stability of α-fluorocyclopropyl radical[31] may be interpreted on a similar ground. The electron withdrawal by a fluorine substituent reduces the importance of repulsion between bonding electrons thus making the hybridization energy the determining factor of the structure. A refined molecular orbital calculation may support the present arguments. It has been shown that the hypothetically strained methyl radical took a pyramidal structure.[33]

From the discussion presented above it is strongly anticipated that both the nonplanarity of a strained (nonbridgehead) radical and the local symmetry stabilizing effect on a strained bridgehead radical have a same principle in commom.

6.5 Experimental

1-Bromobicyclo[2.2.2]octane (1a)

A mixture of 30g of 1-carbethoxy-1,3-cyclohexadiene[34] and 80g of acrolein was heated at 150° under reflux for 90 hr. Distillation at 100-110°/1.5mmHg afforded 19g (47%) of the Diels-Alder adduct 5, which was hydrogenated in an equal volume of acetic acid at atmospheric pressure in the presence of platinum oxide. After removal of the catalyst and most of the solvent 15g (in three portions) of DTBP was added and the mixture was heated at 130° for 20 hr under dry oxygen

free nitrogen. Distillation at 98-100°/10mmHg (lit. 96-98°/12mmHg[34], 75-76°/3 mmHg[35]) afforded 8.1g (49%) of the decarbonylated ester 7, which was hydrolyzed[34] to give 1c in a yield of 96%. According to the reported procedure[16] 1a was prepared in ca. 50% yield by the Hunsdiecker reaction of 1c; mp 61-62° (lit. 58.5-59.5°[36], 66-68°[34]); ir(KBr): 1457, 968, and 815 cm^{-1}; nmr:($CDCl_3$) τ 7.53-8.00 (6H, m, methylene vicinal to Br) and 8.00-8.53 (7H, m, other methylene and bridgehead); mass spectrum: m/e 190 and 188 (M^+, relative intensity 5.6), 109 (100), and 81 (40).

1-Bromobenzobicyclo[2.2.2]octene (2a)

A mixture of benzenediazonium-2-carboxylate (from 10g of anthranilic acid and 20 ml of iso-amyl nitrite[36]) and 200 ml of sodium dry anisole was heated at 70° for 15 hr. The anisole was expelled and the residue was distilled. A fraction boiling at 104-105° /6 mmHg was collected (4.3g), which was a mixture[37] of the 1,4-adduct 8 and benzobicyclo[2.2.2]octadien-2-one[38] (approximately 6:1). The mixture was hydrogenated in methanol at atmospheric pressure in the presence of palladium charcoal. The catalyst was removed by filtration and a calculated amount of tosylhydrazine was added. The mixture was refluxed for 15 hr to convert the undesired ketone to the hydrazone and then passed through a silica gel column. After removal of methanol the residue was distilled at 107°/2.7 mmHg to give 2.9g of 8; ir(neat) 1330, 1163, 1123, 1102, 1070, 1060, and 746 cm^{-1} ; nmr ($CDCl_3$) τ 2.30-2.95 (4H, m, aromatic), 6.45 (3H, s, methyl), 7.05 (1H, broad s,bridge-

head), and 7.80-8.75 (6H, m with peaks at 7.97, 8.13, 8.42, and 8.57, methylene). To an ice-cooled mixture of 500mg (2.6 mmoles) of 8 and 640mg (5.2 mmoles) of acetyl bromide was added ten drops of anhydrous stannic chloride. The mixture was stirred at room temperature for 3 hr and at 80° for 15 hr, poured on ice and extracted with methylene chloride. The methylene chloride was distilled off and the residue was chromatographed on a silica gel column. Elution with petroleum ether gave 140mg of a mixture of the bromide 2a and the chloride 2d (1:1.5). Further elution with petroleum ether-methylene chloride (1:1) afforded 220mg of the acetate 2e. The pure 2a was obtained by means of preparative glpc after the column chromatographic separation of 2e. When stannic bromide was used instead of stannic chloride, 2a and 2e were obtained in a ratio of 1:3 but in much lower total yield.

2a had mp 83.5-84.5°; ir(KBr) 962, 898, 860, 747 cm^{-1}; nmr ($CDCl_3$) τ 2.17-2.47 (1H, m, aromatic (peri)), 2.53-2.97 (3H, m, other aromatic) 6.95 (1H, broad s, bridgehead), and 7.20-8.83 (8H, m with major peaks at 8.02 and 8.22, methylene); mass spectrum: m/e 238 and 236 (M^+, 6.0) 210 and 208 (40), 157 (46.7), and 129 (100).

2d had ir(neat): 1035, 970, 913, 872, 755, 737, and 697 cm^{-1}; nmr ($CDCl_3$) τ 2.20-2.60 (1H, m, aromatic (peri)), 2.60-3.00 (3H, m, other aromatic), 7.00 (1H, broad s, bridgehead), and 7.40-8.80 (8H, m, methylene); mass spectrum: m/e 194 (M^+, 26), 192 (M^+, 73), 166 (32), 165 (49), 164 (64), 163 (67), 129 (100), 128 (76), and 127 (53).

2e had ir(neat): 1740, 1248, 1092, 1040, and 750 cm^{-1}; nmr ($CDCl_3$)

τ2.55-3.00 (4H, m, aromatic), 7.02 (1H, broad s, bridgehead), 7.78 (3H, s, methyl), and 7.30-8.65 (8H, m with peaks at 7.45, 7.90, 8.06, and 8.28); mass spectrum: m/e 216 (18), 174 (100), 146 (84), and 145 (76).

1-Bromodibenzobicyclo[2.2.2]octadiene (3a)

To a solution of 5g of 9-bromoanthracene and 50mg of 2,5-di-tert-butylhydroquinone in 150 ml of chlorobenzene in an autoclave was introduced ethylene to a pressure of 60 atm. The mixture was heated at 150° for 40 hr under stirring (maximal pressure was 110 atm). After distillation of most of the chlorobenzene the residue was chromatographed on a silica gel column. 3a was obtained by elution with petroleum ether. Three recrystallizations from petroleum ether gave ca. 2g of pure 3a in white powder ; mp 137.5-138°; ir(KBr): 1457, 1300, 1160, 1140, 1030, 915, 823, 755, and 738 cm^{-1}; nmr ($CDCl_3$) τ 2.10-2.5- (2H, m, aromatic (peri)), 2.57-3.05 (6H, m, other aromatic), 5.67 (1H, broad s, bridgehead), 7.55-7.95 (2H, m, methylene vicinal to Br), and 7.95-8.35 (2H, m, other methylene); mass spectrum: m/e 286 and 284 (M^+, 6.1), 258 and 256 (100), 205 (3.8), 204 (7.0), 203 (10), 202 (12), 177 (25), and 176 (32).

1-Bromotribenzobicyclo[2.2.2]octatriene (1-Bromotriptycene 4a)

A mixture of 3g of 9-bromoanthracene and benzenediazonium-2-carboxylate (from 8.2g of anthranilic acid and 16 ml of iso-amyl nitrite) in 240 ml of ethylene chloride was heated at 70° for 15 hr. Evaporation of the solvent gave a tarry material, which was chromato-

graphed on a silica gel column. Crude 4a eluted with benzene was repeatedly washed with petroleum ether to remove unreacted 9-bromoanthracene. Pure 4a (1g) was obtained in white powder by recrystallization from benzene; mp 253-254.7° (lit[39] 246-248°); ir(KBr) 1450, 1290, 1155, 1033, 925, 850, 840, 820, and 738 cm^{-1}; nmr ($CDCl_3$) τ 2.10-2.35 (3H, m, aromatic (peri)), 2.45-3.15 (9H, m, other aromatic), and 4,53 (1H, s, bridgehead); mass spectrum: m/e 334 and 332 (M^+, 37) and 253 (100).

Reductive Debromination

A solution of ca. 30mg of a bromide (1a, 2a, 3a, or 4a), ca. 300mg of methyldichlorosilane, a catalytic amount of DTBP in 3 ml of cyclohexane was degassed and sealed. The mixture was heated at 120° for 1-3 hr. The crude reaction mixture was then analyzed by glpc. Identification of the product (1b, 2b, 3b or 4b) was made on the basis of the glpc retention time and ir spectrum. Authentic 1b was obtained by the procedure of Doering.[17] All other authentic hydrocarbons (2b, 3b, and 4b) were prepared by the addition of benzyne to benzene,[21] naphthalene,[21] and anthracene,[20] respectively, followed by hydrogenation if necessary (in the case of 2b and 3b). Controlled experiments showed that the reaction did not take place at all in the absence of DTBP.

The relative disappearance rates were measured by glpc analysis of competitive reactions between a bromide (1a, 2a, or 4a) and 3a (standard) using appropriate standards. The relative rates obtained

were average values of several runs in which the conversion ranged from 30 to 50%. The accuracy of the glpc analysis was carefully checked and it was found that the analytical errors were small enough compared with the differences in the reactivities of the bromides.

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Chapter 7

Origin and Nature of Steric Effects on Hydrogen Abstraction Reactivities of 1-Substituted Adamantanes by Free Radicals

7.1 Summary

Free radical N-bromosuccinimide bromination of a series of 1-substituted adamantanes was carried out and the substituent effects on reactivities of 2,3, and 4 positions were investigated. The bridgehead (3 position) reactivities were correlated with the Taft's equation. On the other hand, a large steric effect was found to contribute to the reactivities of 2 and 4 positions. The steric deceleration on the 4 position was understood in terms of steric interaction between the parent skeleton and a substituent induced by a rehybridization at a remote position and it was possible to correlate the reactivity of the 4 position with a two parameter equation (one parameter was electronic and the other steric). A bulky 1-substituent such as tert-butyl inhibited the 2 hydrogen abstraction almost completely. Such a steric effect was also found in the free radical chlorination of 1-alkyladamantanes with carbon tetrachloride, where a sharp decrease in the reactivity of the 2 position was observed in going from methyl, ethyl, iso-propyl to tert-butyl.

7.2 Introduction

Chemical reactivities can approximately (and empirically) be formulated by several isolated effects, each of which can usually be evaluated quantitatively by using idealized (and simplified) model compounds or systems. Remarkable rigidity and high symmetry of adamantanes has driven us to use them for the model system for the general solution of the structure-reactivity problem in free radical reactions of aliphatic compounds.[1)]

Choice of an appropriate model series is of essential significance in such a study. Thus, reactivities of bridgehead positions of different degrees of bridgehead planarities may afford important information about the effects of strain on carbonium ion[2)] or radical[3)] stabilities. Whereas, a rigid molecule, e.g. adamantane, having a substituent at definite angle and distance from the reaction center may provide a possibility of estimation of polar effect in solvolysis[4)] or free radical[5)] reaction in a saturated aliphatic system. In fact, Gleicher[5)] has shown that the bridgehead hydrogen abstraction from a series of 1-substituted adamantanes was mainly controlled by the polar effect. Correlation of the logarithmic rates with the σ^* value of a substituent was satisfactory. At that time, however, it was unsuccessful to separate the two regio isomers, i.e., 2 and 4 bridge products and there was found no way of simple rationalization about the substituent effects on the bridge positions. The authors have

strongly felt that concurrent operation of polar and steric effects might be responsible for the observed reactivities of bridge positions.

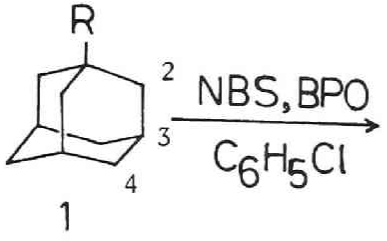
Without exception of adamantane, there seems to be no systematic study on the substituent effects on generation of secondary radicals. The present study reveals novel steric effects of a 1-substituent of adamantane on the free radical reactivity of the remore 4 as well as 2 positions. This kind of steric effects may be of general importance for reaction of polycyclic compound containing substituent.

7.3 Results

Products

Free radical bromination of a series of 1-substituted adamantanes with N-bromosuccinimide (NBS) was carried out at 80° in the presence of benzoyl peroxide (BPO) as an initiator in chlorobenzene under nitrogen. Substituents investigated were methyl, tert-butyl, carbomethoxy, bromo, fluoro, and cyano. As may be seen easily, adamantane nucleus has four different types of abstractable hydrogens. Of the four corresponding products (2,3,4-syn, and 4-anti) the last two are axial-equatorial stereoisomers.

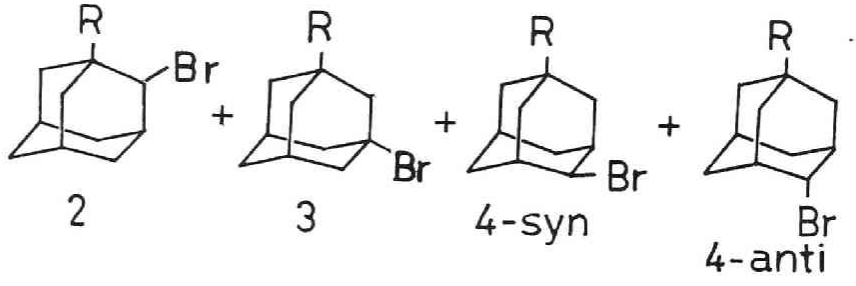
Glpc analysis of the crude bromination mixture of 1-methyladamantane showed the major peak followed by two minor peaks of poor separation in the ordinary glpc analysis condition. The major one was easily assigned as the bridgehead bromide (3a).[6] Clear distinction between the bridge bromides was made on the basis of glpc coinjection (Goley



a $R=CH_3$ d R=Br

b $R=tert\text{-}C_4H_9$ e R=F

c $R=CO_2CH_3$ f R=CN



column) and spectral identity with those of authentic 1-methyl-2-bromoadamantane (2a)[7] and 1-methyl-4-bromoadamantane (4a-syn and 4a-anti); the latter was prepared from 1-methyladamantan-4-one[8] via lithium aluminum hydride reduction followed by thionyl bromide bromination of the resultant alcohol. Careful examination (nmr and glpc) of the bromination mixture of 1-methyladamantane confirmed the absence of any other isomer of methylbromoadamantane such as 1-bromomethyladamantane[9] or 1-bromohomoadamantane.[10]

The bromination of 1-tert-butyladamantane gave the bridgehead bromide (3b) and two minor bromides which were assigned as the 4 bromides (4b-syn and 4b-anti). Interestingly, no detectable amount of the 2 bromide (2b) was formed.*) No evidence was obtained for the tert-butyl hydrogen abstraction.

(*) The 2-bromide (2b) and 4-bromides may easily be distinguished on the basis of nmr chemical shift of the α proton. An additivity

relationship of the α proton chemical shift has been observed for a number of 1-alkyl-2-bromoadamantanes and 1-substituted-4-bromoadamantanes, although such an additivity relationship was no longer applicable to 1-substituted-2-bromoadamantanes having polar 1-substituents (halogen or cyano).[14] Thus, in the present case 2b may have the α proton chemical shift ca. 0.2 ppm higher than those of 4b-syn and 4b-anti.

Glpc analysis of the crude bromination mixture of 1-carbomethoxy, bromo, fluoro, or cyanoadamantane showed a major peak followed by three minor peaks. Without exception, the first eluted, major one was determined as the corresponding bridgehead bromide (i.e., 1-substituted-3-bromoadamantane) (3c,[10] 3d,[11] 3e,[5a] or 3f[5a]). Identification of the bridge bromides was also made by comparing the glpc retention times and spectra with those of the compounds of relevant syntheses. For the purpose, all of the bridge bromides except 1-fluoro-2-bromoadamantane (2e) were prepared independently from 1-carboxyadamantan-2-one[12] (2c, 2d, and 2f), from 4-protoadamantanone (2d[13]), from 1-acetyl-4-acetoxyadamantane[14] (4c and 4f), from 1-fluoroadamantan-4-one[14] (4e), or from 1-bromoadamantan-4-one[15] (4d). Details of most of the preparations have been reported elsewhere.[14]

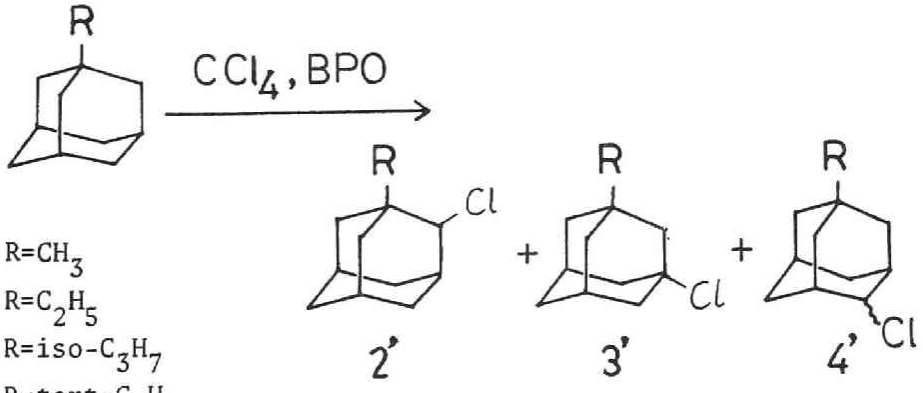
Interestingly, the order of glpc elution of three bromide isomers from a silicone column was dependent on the 1-substituent. In the case of 1-carbomethoxyadamantane, the 2-bromide (2c) had the shorter retention

time than those of the 4-bromides (4c-syn and 4c-anti), while the reverse was true for 1-bromo, fluoro, or cyanoadamantane.

A modest stereoselectivity was observed for the atom transfer to the 4 radical. The observed stereoisomer ratio ranged from 1.1 to 1.3 in all the cases investigated, practically independent on the 1-substituent. Determination of syn and anti isomers was not attempted because both of the stereoisomers (4-syn and 4-anti) originated from the same 4 radical, the relative formation rate of which was the major interest. Thus, these were not treated separately but averaged for the present purposes.

Relative yields of the bromides at very early stage of the reaction were determined by the glpc analysis coupled with nmr integration and is shown in Table I.

Free radical chlorination of 1-alkyl (methyl, ethyl, iso-propyl, or tert-butyl) adamantanes with carbon tetrachloride were carried out similarly in the presence of BPO at 80° under nitrogen. The percentage of the bridgehead chloride (3') was easily determined by a glpc analysis.



a R=CH_3
b R=C_2H_5
c R=iso-C_3H_7
d R=tert-C_4H_9

Table I. Product Distributions and Relative Reactivities of Free Radical Bromination of 1-Substituted Adamantanes with NBS.[a)]

R	Product Distribution (%)[b)] 2	3	4	2/4	$\sigma^*_{CH_2R}$	Relative Disapp Rate[c)]
tert-C_4H_9	~0	88	12	~0	-0.16	2.70
CH_3	17	58	25	0.68	-0.10	2.55
H	55	45			0.00	4.35[d)](3.70[e)]))
CO_2CH_3	13	68	19	0.68	0.71	1.00[f)]
Br	10	62	28	0.36	1.00	0.72
F	9	65	26	0.35	1.10	0.78
CN	9	61	30	0.30	1.30	0.53

a) In chlorobenzene at 80° in the presence of BPO under nitrogen.

b) Errors are within ± 2%.

c) Errors are within ± 9%.

d) Statistically uncorrected.

e) Statistically corrected.

f) Standard.

The distinction of 2' and 4' was also made on the basis of the assumed additivity relationship[14] of the chloromethine proton chemical shift in a 1-alkyl-n-haloadamantane (n=2 or 4)[14]. The observed chloromethine proton chemical shifts are shown in Table II. The predicted chemical shifts based on the substituent shift additivity are also shown.[16]

Table II. Chloromethine Proton Chemical Shifts (τ)[a]

R	CH_3	C_2H_5	iso-C_3H_7	tert-C_4H_9
2'	6.00	5.94		
	(6.00)	(5.98)		
4'	5.77	5.78	5.74	5.78
	(5.80)	(5.74)	(5.79)	(5.88)

a) In carbon tetrachloride with TMS as a standard. Predicted chemical shifts are shown in parentheses.

A rough estimation of the product distribution thus obtained by glpc peak area coupled with nmr integration of the chloromethine proton is summarized in Table III

Table III. Product Distributions and Relative Reactivities of Free Radical Chlorination of 1-Alkyladamantanes with Carbon Tetrachloride[a)]

R	Product Distribution (%)[b)] 2'	3'	4'	Relative Disapp Rate[c)]
H	14	86		1.00
CH_3	8	84	9	0.79
C_2H_5	5	87	9	0.78
iso-C_3H_7	~0	93	7	0.79
tert-C_4H_9	~0	94	7	0.86

a) At 80° in the presence of BPO under nitrogen.

b) Rough estimates based on glpc and/or nmr analyses of not well resolved peaks.

c) Errors are within ±6%.

Relative Reactivities

With the knowledge of product distributions (Table I and III) and relative reactivities per molecule as obtained by relative rates of disappearance of two adamantanes under competitive condition, the relative reactivities per hydrogen atom at 2, 3, and 4 positions can be determined and are shown in Table IV and V.

Table IV. Reactivities of 2, 3, and 4 Positions of 1-Substituted Adamantanes Relative to Those of 1-Carbomethoxyadamantane in NBS Bromination.

	R						
Position	tert-C_4H_9	CH_3	H	CO_2CH_3	Br	F	CN
3	3.50	2.25	2.16[a]	1.00	0.672	0.746	0.475
2	~0	3.33	9.23	1.00	0.554	0.540	0.366
4	1.71	3.09	6.32	1.00	1.06	1.07	0.838

a) Statistically corrected.

Table V. Reactivities of 2, 3, and 4 Positions of 1-Alkyladamantanes Relative to Those of Adamantane in Carbon Tetrachloride.

	R				
Position	H	CH_3	C_2H_5	iso-C_3H_7	tert-C_4H_9
3	1.0	1.0[a]	1.1	1.1	1.3
2	1.0	0.9	0.6	~0	~0
4	1.0	1.0	0.9	0.9	0.9

a) Statistically corrected.

7.4 Discussion

Bridgehead Reactivities

As shown in Figure 1, the logarithmic relative rates of the bridgehead (3 position) hydrogen abstraction by bromine atom*) (from NBS) can be correlated with the Taft's equation. A ρ^* value of -0.51 (r=0.9843) was obtained in agreement with Gleicher's ρ^* (-0.59),[5b] which was understandable in terms of the interaction between a carbon-substituent dipole and partial positive charge developing at the

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(*) Bromine atom is well documented to be the chain carrier in the free radical NBS bromination,[17] although some new data show that the mechanism of radical brominations by molecular bromine and NBS are different. Hydrogen abstraction by initiator-derived radicals may be unimportant at least under the present reaction condition. This conclusion was drawn by the fact that any oxygenated adamantane was not formed appreciably when a chlorobenzene solution of adamantane and a large amount of BPO was heated under vigorous flow of oxygen although autoxidation of adamantane could take place under more vigorous conditions (high pressure[18]) or by use of a more effective initiator (di-tert butyl peroxide[14]), indicating that under present condition BPO-derived radicals could not abstrac hydrogen from adamantane giving the bridgehead radical appreciably.

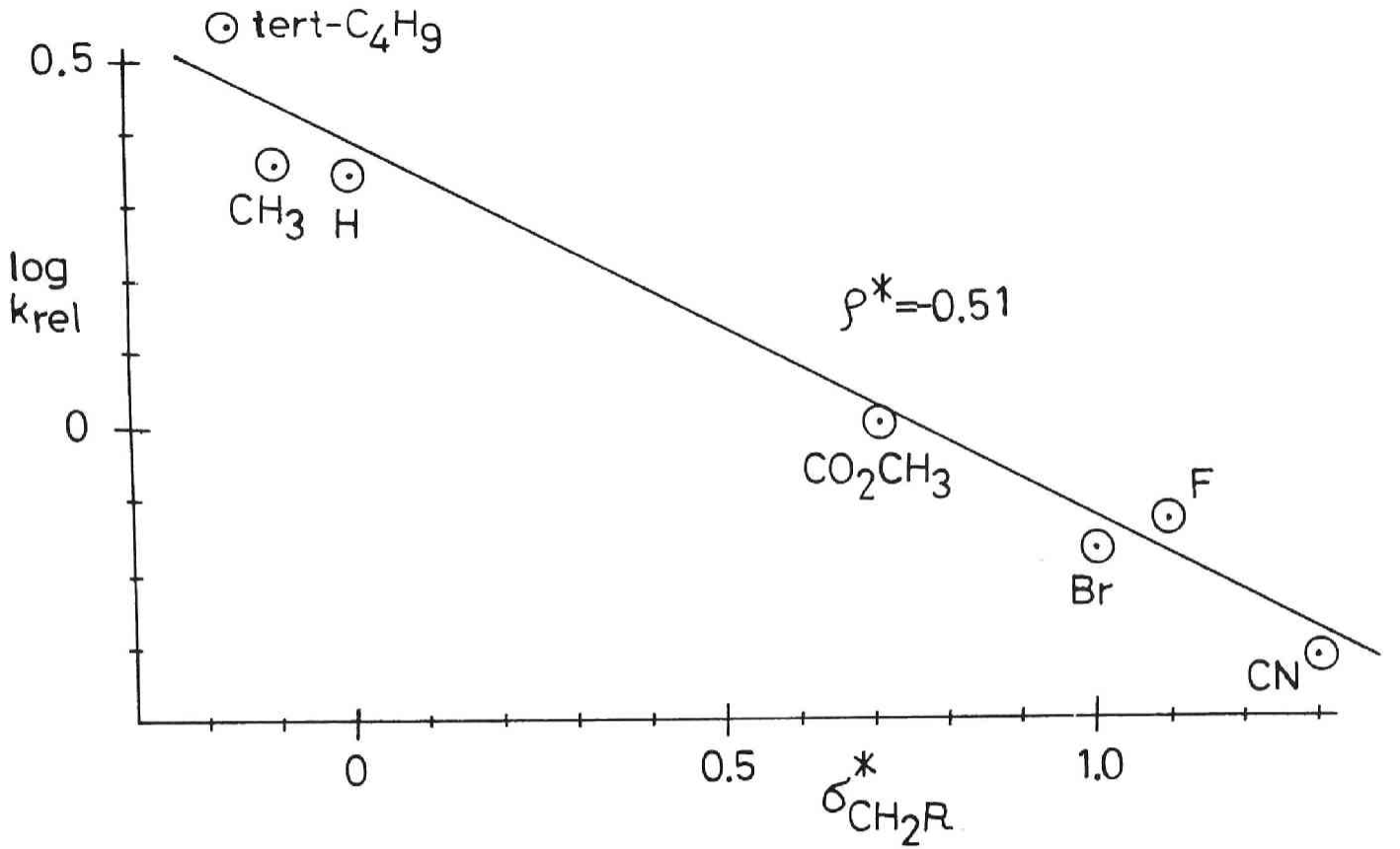
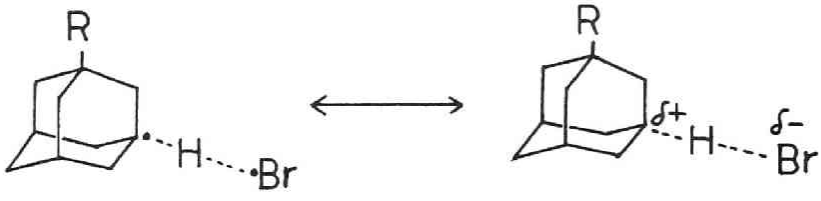


Figure i. Correlation of relative rates of the bridgehead hydrogen abstraction by bromine from 1-substituted adamantanes with $\sigma^*_{CH_2R}$

reacting carbon atom in the transition state of hydrogen abstraction by an electron deficient radical.



Reactivity of 2 Position

A claim of the operation of polar effect on hydrogen abstraction from an aliphatic substrate comes from the observation that an electronegative substituent causes reduced reactivity of the vicinal hydrogen compared with the remote hydrogen in an open chain or cyclic system.[19] In the NBS bromination of adamantanes, a general trend is observed that the 2 position has always a lower reactivity than the 4 position. In the case of polar 1-substituent, the reactivity ratio of 2 to 4 ranged from 0.30 to 0.68 (Table I), which may be compared with the 2 to 4 reactivity ratio in the free radical chlorination of a substituted cyclohexane; ratio (substituent, reagent), 0.3-0.44 (Cl, Cl_2 +hν),[19d] 0.2-0.24 (Br, Cl_2+hν),[19d] 0.4 (Br, tert-C_4H_9OCl),[19d] 0.3-0.35 (CO_2H, Cl_2+hν),[19e] and 0.47 (CO_2CH_3, SO_2Cl_2).[19f] However, a simple correlation with the polar effect of a substituent could not be applied successfully to the reactivity of 2 position, in marked contrast to the bridgehead reactivity. Remarkably reduced reactivity

(relative to adamantane) of 2 positions of 1-alkyladamantanes toward hydrogen abstraction by bromine (Table IV) or trichloromethyl (Table V) may be the most convincing evifence for a steric retardation. The bulky tert-butyl inhibits the 2 hydrogen abstraction almost completely. Even the methyl shows an appreciable retardation in the case of NBS bromination (Table IV). Although a steric deceleration is often referred to when an electron donating group shows a rate depression in an electrophilic hydrogen abstraction,[1e,20] assessment of steric effect on a quantitative basis may sometimes be not easy because of concurrence of a polar effect of a substituent. In this respect the reactivities of the 2 positions of 1-alkyladamantanes toward hydrogen abstraction by trichloromethyl may present an ideal model for the investigation of steric effect, for the contribution of polar effect can be minimized in this case by choice of alkyl groups. An emphasis should be made on the observed sharp decrease in reactivity in going from methyl, ethyl, iso-propyl, to tert-butyl (Table V).

Thus, a combination of polar and steric effects may be the controlling factor of the reactivity of 2 position toward hydrogen abstraction by bromine and the relative rates might be correlated with two parameters, one is electronic and the other steric, by an equation like the expanded Taft's equation.[21]

Reactivity of 4 Position

The most important and exciting observation in the present study is the highly anomalous change in the reactivity of 4 hydrogen abst-

raction by bromine (Table IV). A large depression by an alkyl group (methyl or tert-butyl) was observed although alkyl groups showed small effects on the reactivities of the 4 hydrogen abstraction by trichloromethyl (Table V). An alkyl group is slightly electron donating[4,5a,22] and thus the present deceleration by an alkyl group on the 4 hydrogen abstraction may reasonably be steric in origin. A 1-substituent, however, which is equatorial to the cyclohexane ring, locates too far from the 4 position to exert any direct steric repulsion on the 4 hydrogen abstraction. A supporting evidence for this claim comes from the study of Price, et.al.,[19f] who found no axial-equatorial selectivity even in the 3 hydrogen abstraction from trans-1-tert-butyl-4-carbomethoxycyclohexane although the 3 axial hydrogen had a closer proximity to the tert-butyl group than the 3 equatorial hydrogen. Another evidence may be obtained in a low stereoselectivity (anti to syn) of atom transfer reaction even to the 1-tert-butyladamantyl-4-radical. Thus, the observed anomaly in the reactivity of 4 position of 1-tert-butyladamantane (ca. 3 fold rate depression) should be attributed to another kind of steric effect, search for the origin of which is also one of the major subjects of the present study.

We must first recognize that any substituent could not be introduced into a molecule without any change in the geometry of the parent molecule. tert-Butyladamantane can never be considered as a simple combination of "rigid" adamantyl and "rigid" tert-butyl.

Unfavorable steric repulsion between tert-butyl hydrogens and hydrogens at 2 position of adamantyl must be involved in this combination. If such a nonbonded repulsion is considerably large, the molecule as a whole would change its geometry to minimize the sum of such steric interactions, where the hypothetical nonbonded interaction energy in "rigid" tert-butyladamantane is "shared" by other possible forms of strain (bond length, bond angle, or torsional strain). The X ray crystallographic structure of 1,1'-biadamantyl[23] may provide a proof for the above consideration.[24]

Appreciable H_2-H_2' nonbonded repulsions in this molecule were evidenced by the considerably stretched C_1-C_1' bond (1.578 A) linking two bridgeheads and the broadening of the C_1'-C_1-C_2 angle (111.5-111.8°). Slight narrowing of the C_3-C_4-C_5 angle (109.0-109.1°) was also observed with a compensating broadening of the C_1-C_2-C_3 angle (111.5-111.8°).*) All of the characteristics about the structure of 1,1'-biadamantyl may safely be applied to 1-tert-butyladamantane because of the structural similarity.*) The energy required for the

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(*) The insensitivity of the C_3-C_4-C_5 angle to the bulky 1-substituent may be attributed to the rigid cage structure. The calculated C-CO-C angle of adamantanone was only 112.5°.[25] A similar value was expected for 1-tert-butyladamantan-4-one from its carbonyl stretching frequency, which was practically the same as adamantanone.[26]

angular distortion at C_4 should be very large. This is an important point for the interpretation of the kinetic result about 1-tert-butyl adamantane. The 1-tert-butyladamantyl-4-radical (which was found to be less readily formed than 2-adamantyl radical) undergoes a broadening of the C_3-C_4-C_5 angle with a compensating (small) narrowing of the C_2-C_1-$C(CH_3)_3$ angle as the $sp^3 \rightarrow sp^2$ rehybridization proceeds. Tert-butyl hydrogens and 2 hydrogens are forced to a closer proximity which results in an increase of nonbonded repulsion energy, thus leading to an overall rate depression.**) Whatever the detailed mechanism may be, the present deceleration of the 4 hydrogen abstraction from 1-tert-butyladamantane is the result of strain increase upon rehybridization. To avoid confusion with the "direct steric repulsion" (or primary steric effect) we should like to designate the present decelerating substituent effect as the secondary steric effect (deceleration originating from steric interaction between parent skeleton and substituent induced by the rehybridization at the

(**) Brown's original back strain theory[27] (although not widely accepted today) bears some (formal) similarity to the present mechanism of rate depression. The low basisity of a tert amine (bond angle of which was found similar to that of a primary or secondary amine) has been attributed to an increase in nonbonded interaction between substituents upon quaternization of the amine.

remote position.

It is interesting to compare the present effect of 1-tert-butyl with the decelerating effect of bridgehead methyl in solvolysis of bridgehead bromoadamantanes.[4,28] Schleyer and woodworth[4] have suggested a slight change produced by methyl substitution in geometry (and therefore hybridization state) of the reacting carbon atom presumably via a steric reason to be responsible for the observed rate depression.

Now, we can, for the first time, treat quantitatively the reactivity of 4 position toward hydrogen abstraction by bromine atom which is a function of the σ^* value (polar effect) and the effective steric effect of a substituent. Assuming that the secondary steric effect of fluorine substituent (the least bulky except hydrogen) is negligible, the difference between the reactivity of adamantane and that of fluoroadamantane can be taken as the result of polar decelerating effect. Then, a rough separation of polar and secondary steric effects on the reactivities of 4 position is possible. Without any steric effect, the plot of the log k_{rel} vs. $\sigma^*_{CH_2R}$ would yield a straight line (Figure 2, broken line). Actually, all of the points except fluorine and cyano were considerably below the broken line, depending on their bulkiness. The differences between the observed and the predicted (from the broken line) reactivities (ΔF_{steric}) are thus ascribed to the secondary steric effect.

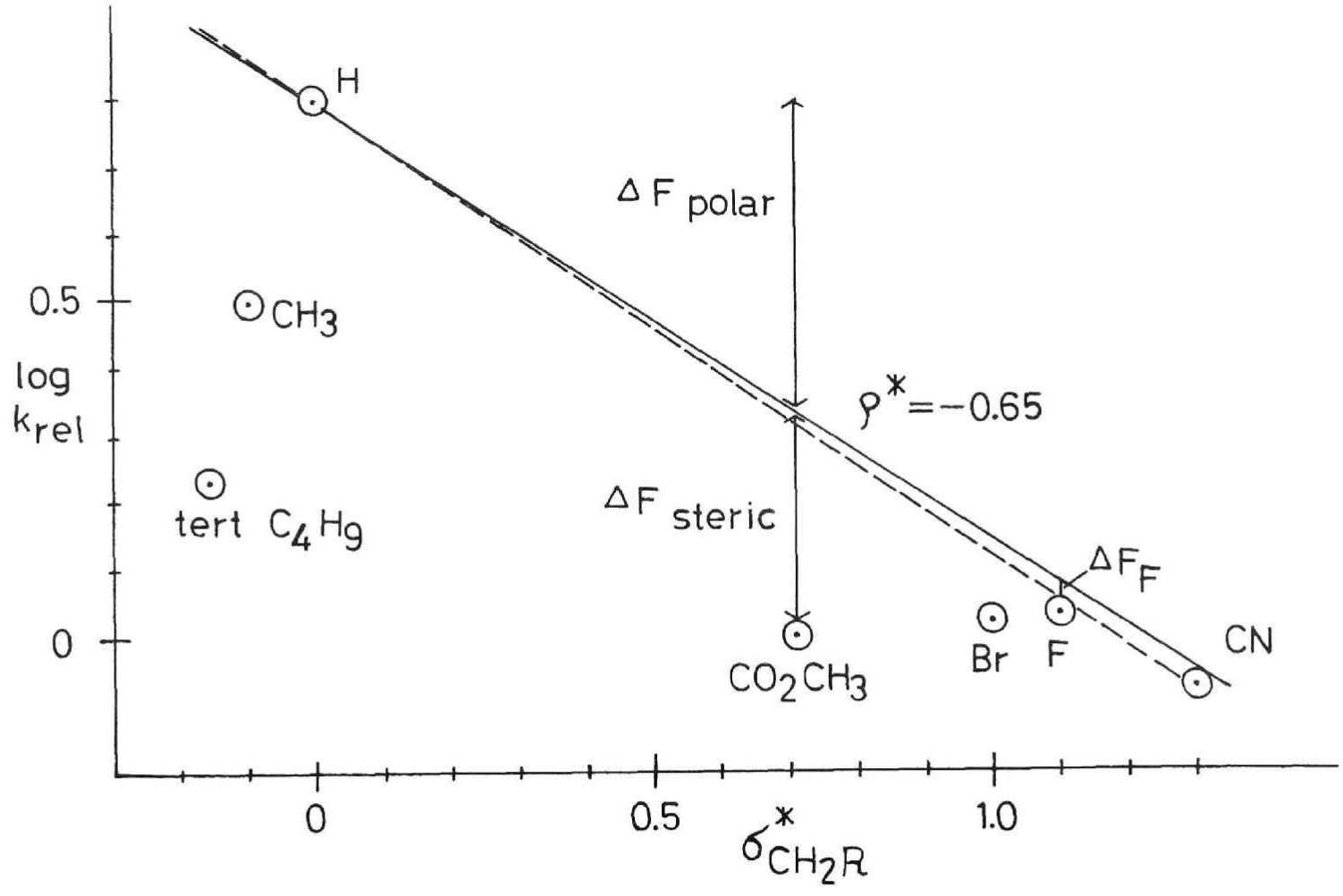

Figure 2. Relative rates of the 4 hydrogen abstarction by bromine from 1-substituted adamantanes vs. $\sigma^*_{CH_2R}$.

Figure 3 shows the linear correlation of the approximate steric destabilization energies so obtained (ΔF_{steric}) with axial-equatorial free energy differences (ΔF_{a-e}) of substituted cyclohexanes,[29,30] an independent measure of the steric requirement of a substituent. The correlation (although poor) may be sufficient for the present

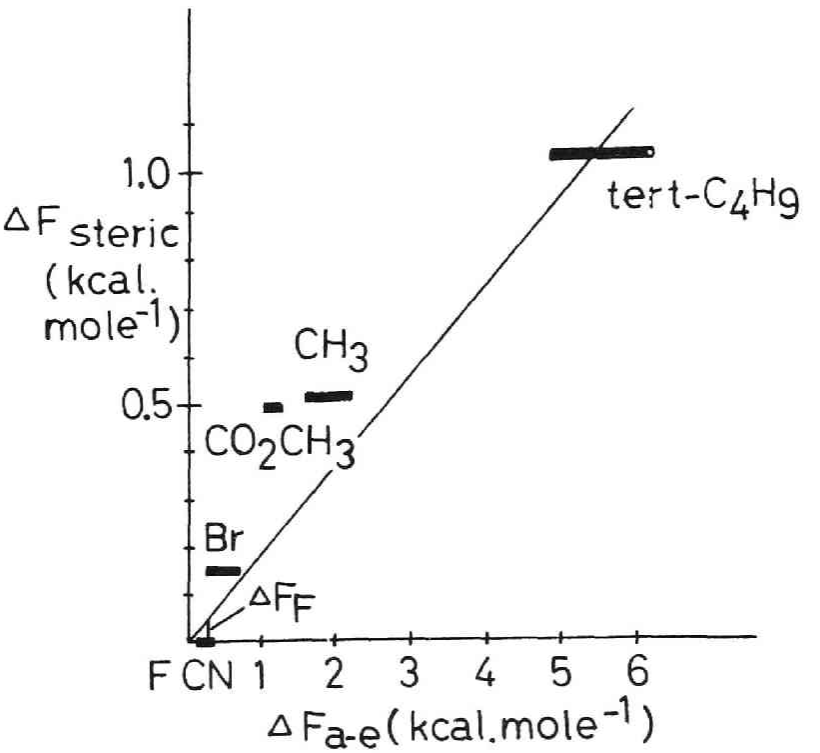

Figure 3. Correlation of the steric destabilization energies with the conformational energies of substituted cyclohexanes.

purpose to know that ΔF_{steric} is steric in origin, although there seems to be no firm basis to expect a good (linear) correlation when it is taken into account that the two quantities are remarkably different in nature, i.e., in that ΔF_{a-e} is related to a thermodynamic while the present ΔF_{steric} to a kinetic quantity and in that the origin of ΔF_{a-e} is a 1,3-diaxial, while ΔF_{steric} is assumed to be 1,2-diequatorial interaction.

The observed ΔF_{steric} for CO_2CH_3 deviates significantly from the line of best fit for other symmetrical substituents (Figure 3). This is presumably because of the lack of symmetry around the carbon bearing the substituent (leading to a general trend of the underestimation of the effective bulk for such an asymmetrical substituent as C_2H_5, iso-C_3H_7, or CO_2CH_3 *) when attached to a cyclohexane ring (by taking least repulsive conformation). The symmetrical nature of the adamantane bridgehead eliminates this uncertainty and asymmetrical CO_2CH_3 is, when attched to adamantane bridgehead, taken as "symmetrical" in respect to the effective bulk. The present destabilization energy (ΔF_{steric}) is an alternative (may be better) measure of the steric requirement of a substituent, since the conformational energy is significantly sensitive to the method of measurement and is not very appropriate to represent actual bulk for asymmetrical substituent.

Steric destabilization energy of fluorine (ΔF_F) or cyano (first approximated to be zero) was obtained as shown in Figure 3. With this

correction of ΔF_F a solid line was drawn in Figure 2, which seemed to be a more accurate representation of the polar effect. The σ* value thus obtained (-0.65) is slightly larger than that for the bridgehead reactivities (-0.51)**). In Figure 2 the total destabilization (ΔF) of ca. 1.2 kcal.mole^{-1} (relative to adamantane) in the hydrogen abstraction at the 4 position of 1-carbomethoxyadamantane can thus be divided into the polar destabilization (ΔF_{polar}) of ca. 0.7 kcal.mole^{-1} and the secondary steric destabilization (ΔF_{steric}) of ca. 0.5 kcal.mole^{-1}.

Thus the relative reactivity of the 4 position toward hydrogen abstraction by bromine can be formulated by an expression

$$\log \frac{k_X}{k_H} = -0.65\ \sigma^* - 0.12\ \Delta F_{a\text{-}e}$$

There still remain two important points to answer about the secondary steric effect. First, why is the secondary steric effect not so big on trichloromethyl attack to the 4 position as on bromine

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(*) $\Delta F_{a\text{-}e}$ for ethyl or iso-propyl is similar to that of methyl, while $\Delta F_{a\text{-}e}$ for symmetrical tert-butyl is quite large, ref 29.

(**) If the Gleicher's modification of the Kirkwood-Westheimer treatment is applied to the observed ρ* values for 3- and 4-reactivities, the partial positive charge developing at the reacting carbon is shown to be greater (ca. 1.5 fold) for the 4 position than for the 3 position

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attach? Second, why is the secondary steric effect not so big on bridgehead reactivities as on bridge reactivities? The first question may be answered in terms of the location of a transition state. According to the Hammond's postulation,[31] the considerably endothermic hydrogen abstraction by bromine (ΔH = 7 kcal.mole^{-1})[32] may have a transition state much more product-like than the nearly thermoneutral hydrogen abstraction by the trichloromethyl (ΔH = -1 kcal.mole^{-1}).[32] Thus, in the transition state of trichloromethyl attack, where planarity is demanded to a lesser extent than that of bromine attack, stabilization via rehybridization is not so important and no appreciable rate depression of the 4 position is observed for trichloromethyl attack (Table V). Any full interpretation should be deferred about the second quetion until more informations are available as to the geometry (especialy around 1-bridgehead) of 1-substituted-3-adamantyl radical*). It is plausible, however, that the rigid structure permitts only a slight conformational change in the bridgehead radical formation compared with a cyclic bridge radical, the formation of the latter is accompanied with $sp^3 \rightarrow sp^2$ structural change via ready movement of much less restricted hydrogen atom.

(*) Recently the esr spectrum of the bridgehead adamantyl radical was reported and a flattening of only ca. 0.1 A at the radical center was suggested.[33]

Thus, the secondary steric effect, if any, may be smaller on the bridgehead reactivities than on the bridge reactivities.

Finally an attempt should be made to analyze the reactivity of the 2 position. The secondary steric effect, shown to be significant on the 4 hydrogen abstraction by bromine, may contribute to the 2 hydrogen abstraction as well. Thus, the reactivity of the 2 position may be governed by a combination of polar, secondary steric, and direct steric repulsion between the substituent and an attacking species. Although magnitude of each contribution is difficult to estimate separately, an approximate ρ^* value may be obtained by, in this case too, neglecting any steric effect for small fluorine or cyano substituent, The observed ρ_2^*/ρ_4^* was 1.63, larger than unity, which may be compared with the ρ_2^*/ρ_4^* of 2.46 predicted from a rough approximation of the Kirkwood-Westheimer treatment[34] assuming that the partial positive charge developing at the reacting carbon in the transition state of the hydrogen abstraction is the same for 2 and 4 positions.*)

(*) If an approximation is made that the effective dielectric const constant is the same for reactions at 2 and 4 positions, a dipole-point charge field model would give

$$\rho_2^*/\rho_4^* = R_4^2/R_2^2 \cos\theta_2/\cos\theta_4$$

where R represents the distance between the midpoint of a substi-

tuent dipole and the reacting carbon and θ the angle between the dipole and the line penetrating the midpoint of the dipole and the reacting carbon. Respective values were obtained from a molecular model.

7.5 Experimental

Materials and Authentic Bromides

1-Methyladamantane[35] was prepared by reduction of 1-dichloromethyladamantane with sodium in methanol.[36] Thus, to a vigorously stirred solution of 5.82g of 1-dichloromethyladamantane[37] in 200 ml of methanol was added in small portions 30g of sodium slice in a period of 3 hr. Then additional methanol (150 ml) was added and the mixture was refluxed for 2 hr. The mixture was concentrated to ca. 100 ml and , after addition of 400 ml of water, extracted with five portions of 50 ml of n-pentane. Pentane was carefully distilled off and the residue (mixture of 1-methyladamantane and 1-dichloromethyladamantane) was again treated similarly as described above to complete the conversion. 1-Methyladamantane (3.6g, 90%) was obtained as a white solid by distillation at 93-95°/45 mmHg.

1-Ethyladamantane was prepared by the Grignard coupling between 1-bromoadamantane and ethylmagnesium bromide.[35b] A byproduct, adamantane, was removed by sublimation.

1-iso-Propyladamantane was obtained by the catalytic hydrogena-

tion of 1-iso-propenyladamantane, which was prepared by the condensation of methyl 1-adamantanecarboxylate and methylmagnesium iodide followed by dehydration.[38]

1-tert-Butyladamantane was prepared by the Grignard coupling between methylmagnesium iodide and 2-(1-adamantyl)-2-bromopropane,[38b] which was obtained by condensation of methyl 1-adamantanecarboxylate and methylmagnesium iodide followed by bromination with phosphorous tribromide.[39] The pure compound was obtained by recrystallization after a byproduct, 1-iso-propenyladamantane, had been removed by fractional distillation.

Methyl 1-adamantanecarboxylate was obtained by the Fischer esterification of the acid which was generated by the Koch-Haaf carboxylation of adamantane.[40]

1-Bromoadamantane was obtained by the bromination of adamantane.[41]

1-Fluoroadamantane was prepared by treating the bromide with anhydrous silver fluoride in hexane under reflux.[16a]

1-Cyanoadamantane was prepared by treating the bromide with cuprous cyanide in pyridine.[5a,42]

1-Methyl-3-bromo (3a),[6] 1-methyl-2-bromo (2a),[7] 1-tert-butyl-3-bromo (3b),[4] 1-carbomethoxy-3-bromo (3c),[10] 1-carbomethoxy-2-bromo (2c),[14] 1-carbomethoxy-4-bromo (4c)[14] 1,3-dibromo (3d),[11] 1,2-dibromo (2d)[13] 1-cyano-2-bromo (2f),[14] and 1-cyano-4-bromoadamantane (4f)[14] were prepared as described. Experimental details of the preparation of 1,4-dibromoadamantane (4d) and 1-fluoro-4-bromoadamantane (4e)

were given in chapter 1.

1-Methyl-4-bromoadamantane (4a)

To a chloroform solution of 1-methyladamantan-4-ol[43] was added excess thionyl bromide at 0°. The mixture was heated at 100° for 2 hr, then washed with aqueous sodium bisulfite, sodium carbonate, and water. After evaporation of the solvent, the residue was distilled at 82-89°/5 mmHg to give 4a as a mixture of syn and anti derivatives; ir(neat) 1060, 970, 955, 940, 893, and 730 cm^{-1}; nmr (CCl_4, TMS) τ 5.50 (1H, broad s, CHBr), 9.15 and 9.21 (in a ratio of ca. 1.4:1, 3H, s, CH_3), and 7.4-8.7 (13H, m with peaks at 7.5, 7.8, 8.05, 8.35, and 8.5, remaining adamantyl protons)

1-Methyl-4-bromoadamantane (4a) and 1-Methyl-2-bromoadamantane (2a)

A solution of 1-methyladamantane (2.5g), NBS (3g), and BPO (0.4g) in chlorobenzene (20 ml) was stirred at 80° under nitrogen atmosphere for 10 hr. The cooled solution was washed with aqueous sodium hydroxide and water and dried over sodium sulfate. The solvent and most of unreacted 1-methyladamantane was carefully removed by distillation and the residue was distilled at 85-91°/5 mmHg to give ca. 1.1g of an oil which consisted of 1-methyladamanatne and isomeric 1-methylbromoadamantanes (2a, 3a, and 4a). The bridge bromides (2a and 4a) were separated from the bridgehead bromide (3a) by means of preparative glpc (silicone DC 550).

Anal. (for the bridge bromides' part, which contained a few percent of the bridgehead bromide).

Calcd for $C_{11}H_{17}Br$: C, 57.65; H, 7.48; Br 34.91

Found : : C, 57.69; H, 7.71; Br, 34.63

1-tert-Butyl-4-bromoadamantane (4b)

Free radical bromination of 1-tert-butyladamantane (7g) was carried out similarly as described for 1-methyladamantane. After usual work-up, 3g of isomeric bromide mixture (3b and 4b) was obtained by a column chromatography, which was dissolved in 10 ml of tetrahydrofurane. Silver nitrate (3.9g), pottasium carbonate (5.6g), and water (95 ml) were added and the mixture was refluxed for 2 hr under vigorous stirring and filtered while hot. The inorganic solid was well washed with ether. The filtrate was extracted with three portions of 50 ml of ether. The combined ether extract was washed with water and dried over sodium sulfate. The ether was evaporated and the residue was chromatographed on a silica gel column. Crode 4b (0.2g) was eluted with n-hexane, which was further purified by means of preparative glpc; ir(neat) 1360, 1260, 1195, and 1190 cm^{-1}; nmr (CCl_4, TMS) τ 5.53 (1H, broad s, CHBr), 9.14 and 9.18 (in a ratio of 1.3:1, 9H, s, $C(CH_3)_3$), and 7.5-8.6 (13H, m with peaks at 7.82, 8.21, and 8.40, remaining adamantyl protons); mass spectrum m/e 270 and 272 (relative intensity 1.6), 213 and 215 (52), 135 (100), and 133 (97).

Anal. Calcd for $C_{14}H_{23}Br$: C, 62.36; H, 8.55

Found : C, 62.20; H, 8.48

Further elution with n-hexane-methylene chloride (1:1) gave

1.8g of 1-tert-butyladamantan-3-ol.

1,2-Dibromoadamantane (2d)

According to the procedure of McKervey[13] 2d was prepared from 4-protoadamantanone, phosphorous tribromide, and phosphorous pentabromide. The same compound (2d) was also obtained by the Hunsdiecker reaction of 1-carboxy-2-bromoadamantane.[14] Thus, to a vigorously stirred mixture of 20mg of 1-carboxy-2-bromoadamantane and 30mg of red mercuric oxide in ca. 1.5 ml of 1,2-dibromoethane was added 0.03 ml of bromine at room temperature. The mixture was stirred for 3 hr, then 5 ml of methylene chloride was added and the inorganic material was filtered off. The filtrate was concentrated and the residue was chromatographed on a silica gel column. Elution with pentane gave 7mg of 2d; ir(KBr) 1347, 1288, 1267, 1028, 976, 963, 953, 826, and 681 cm^{-1}; nmr (CCl_4, TMS) τ 5.38 (1H, broad s, CHBr) and 7.0-8.6 (13H, m, remaining adamantyl protons).

Kinetic Runs

Free radical halogenation of a 1-substituted adamantane was carried out similarly as described for adamantane.[1e] The relative disappearance rates were measured by glpc analysis of the competitive bromination or chlorination between two adamantanes using appropriate external standard. The relative rates listed in Table I and III were average values of several runs in which the conversion ranged from 30 to 50%.

7.6 References

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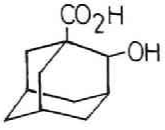
Ir and Nmr Spectra of New Compounds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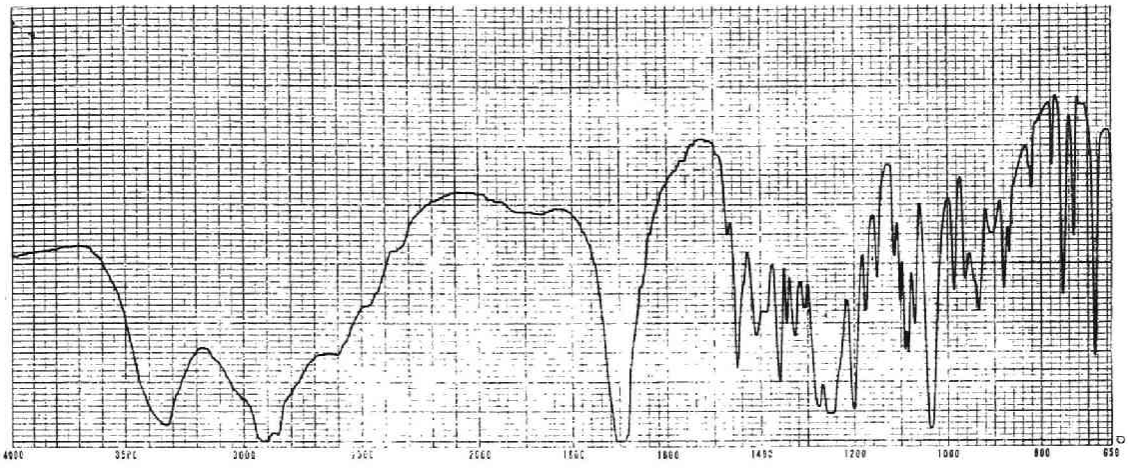

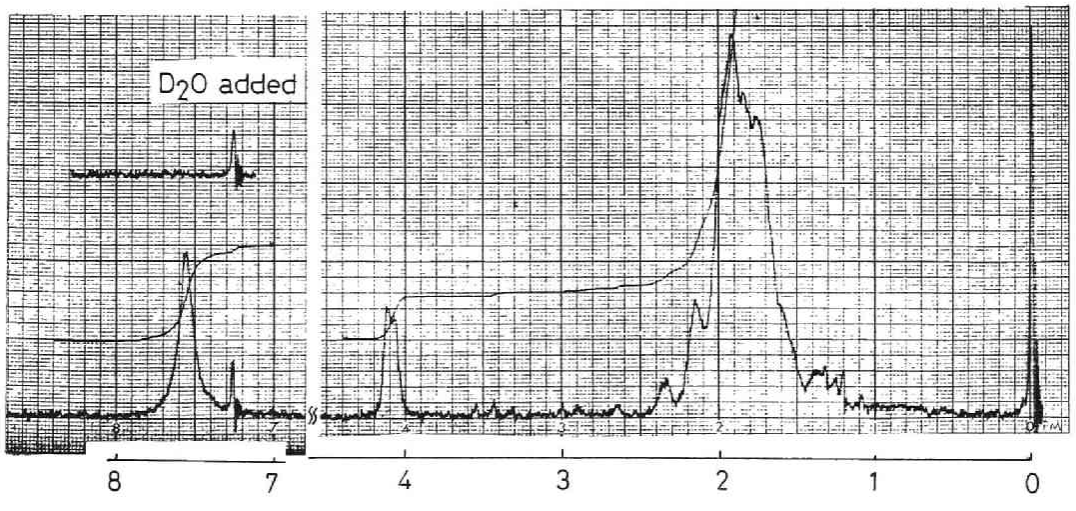
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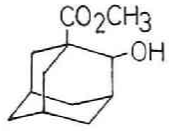
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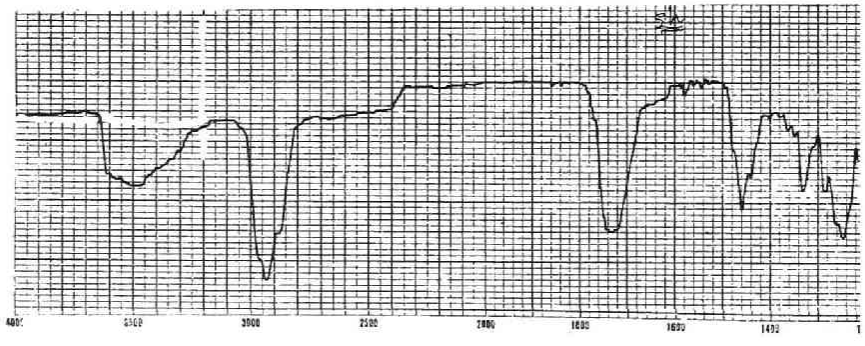

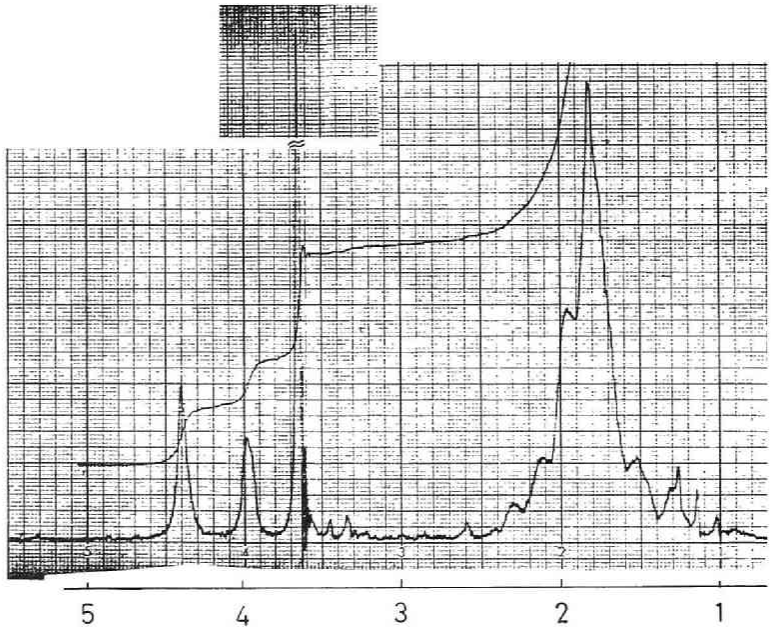
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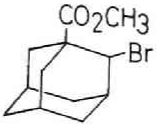
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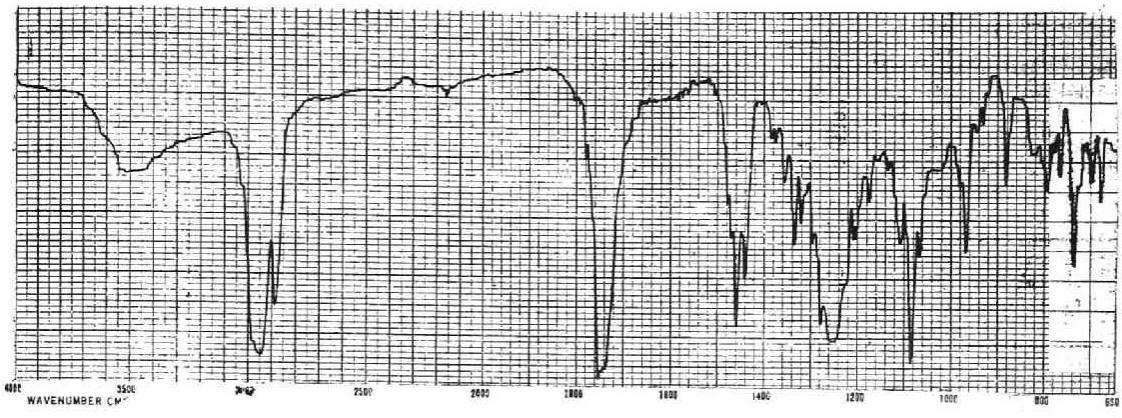
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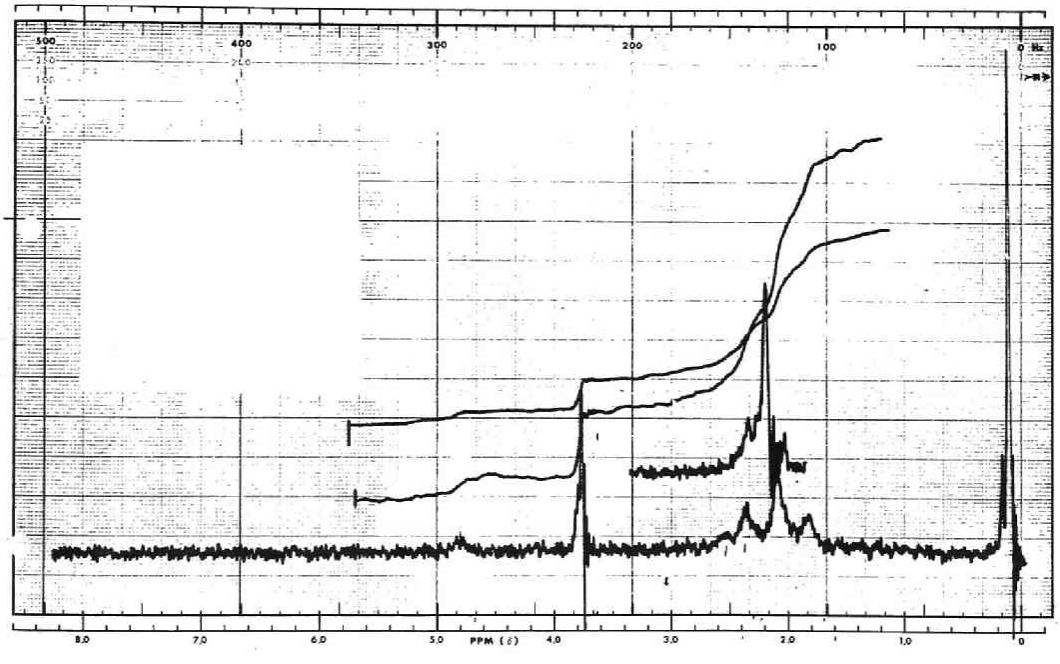
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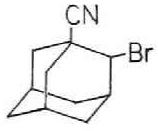
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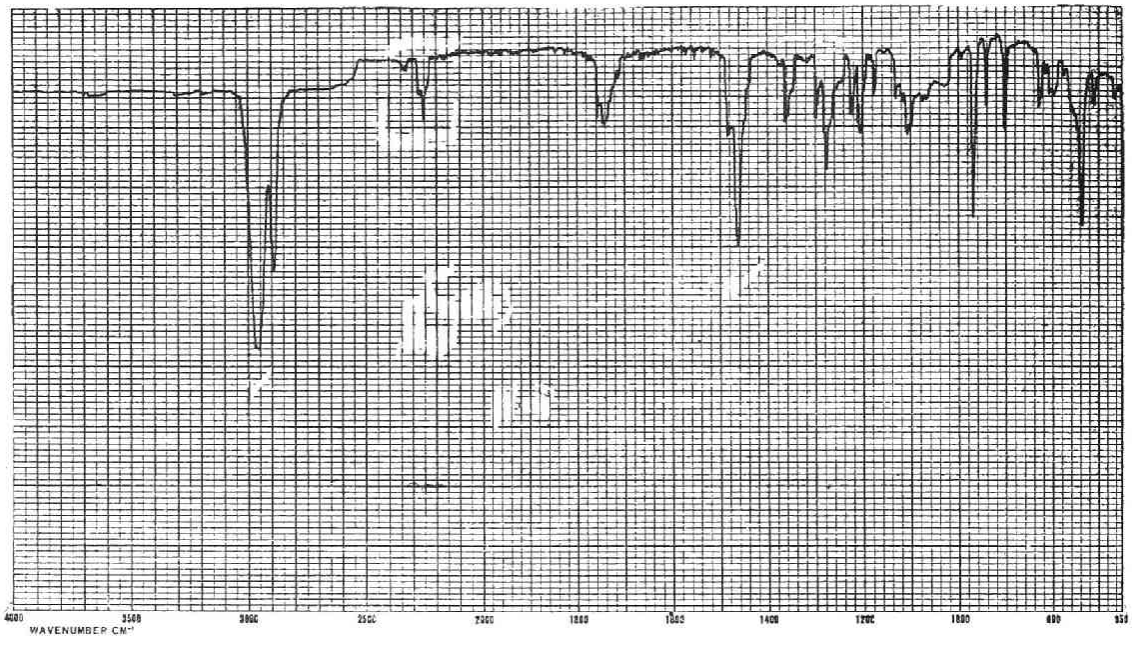
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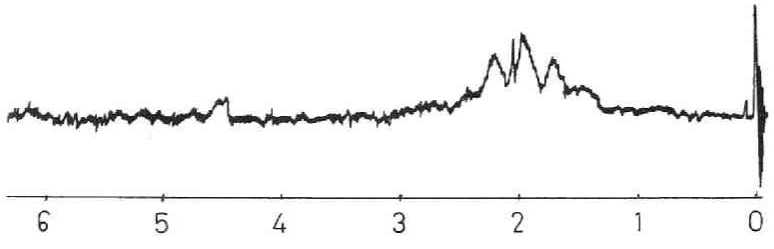
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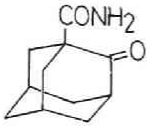
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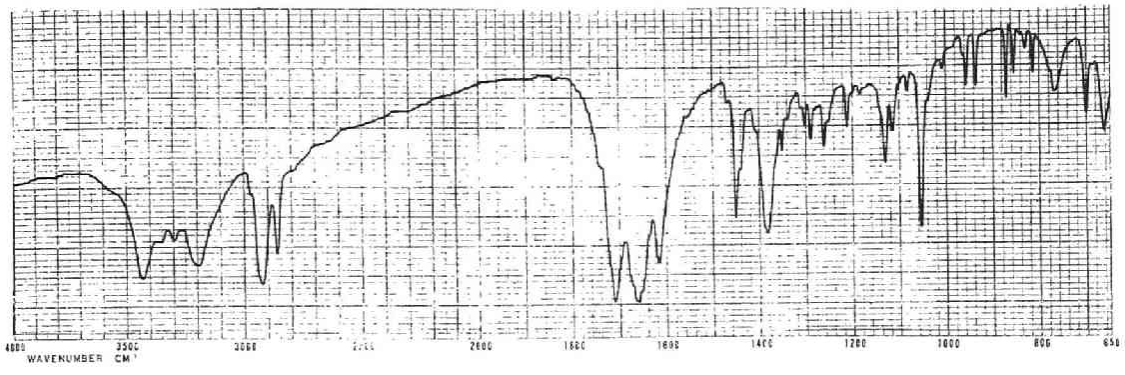
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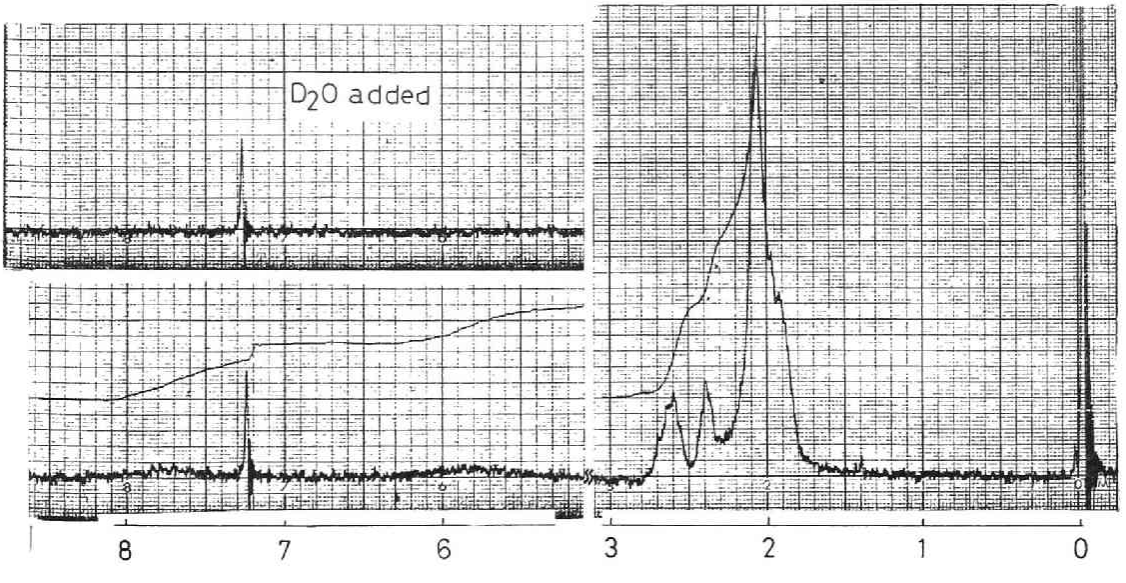
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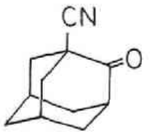
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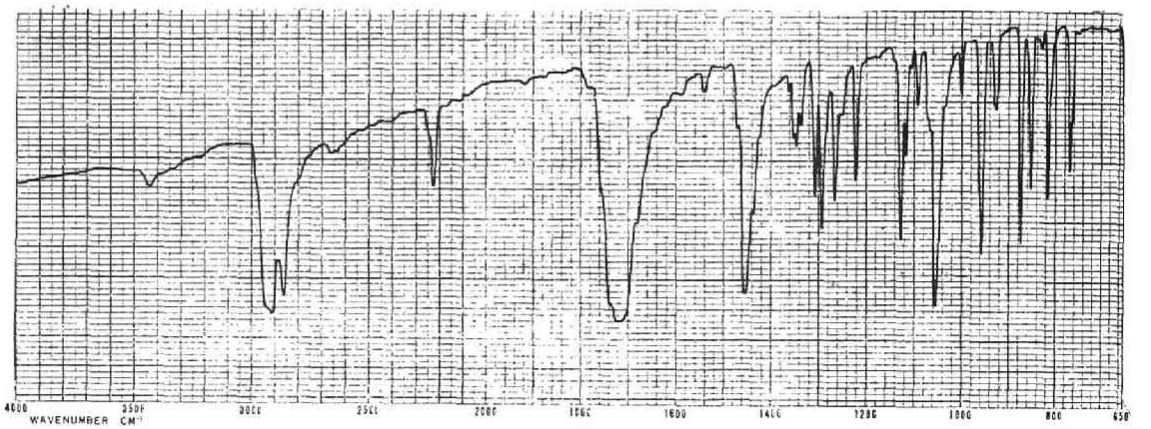
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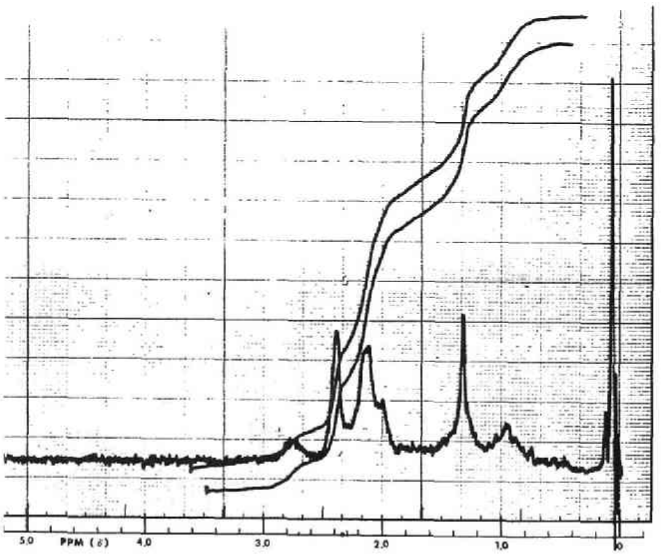
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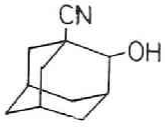
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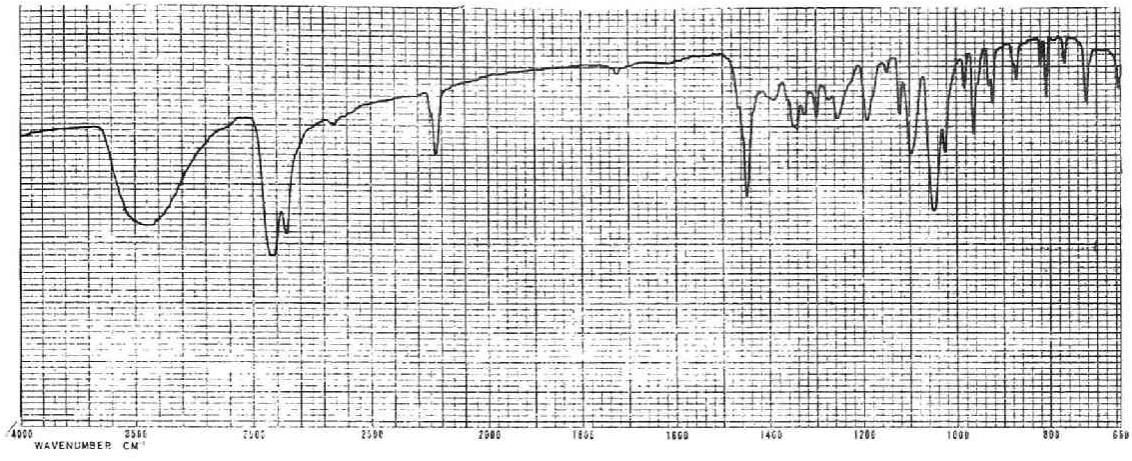
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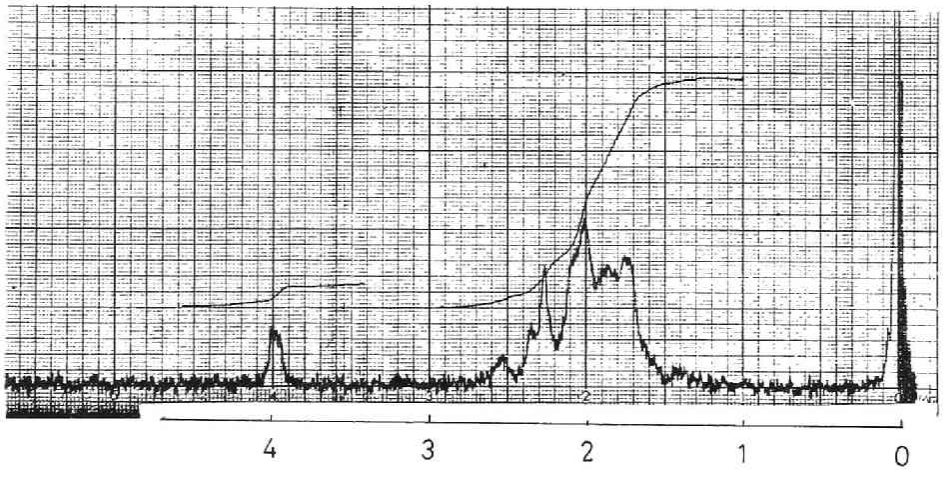
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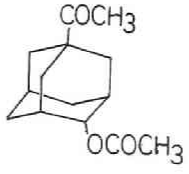
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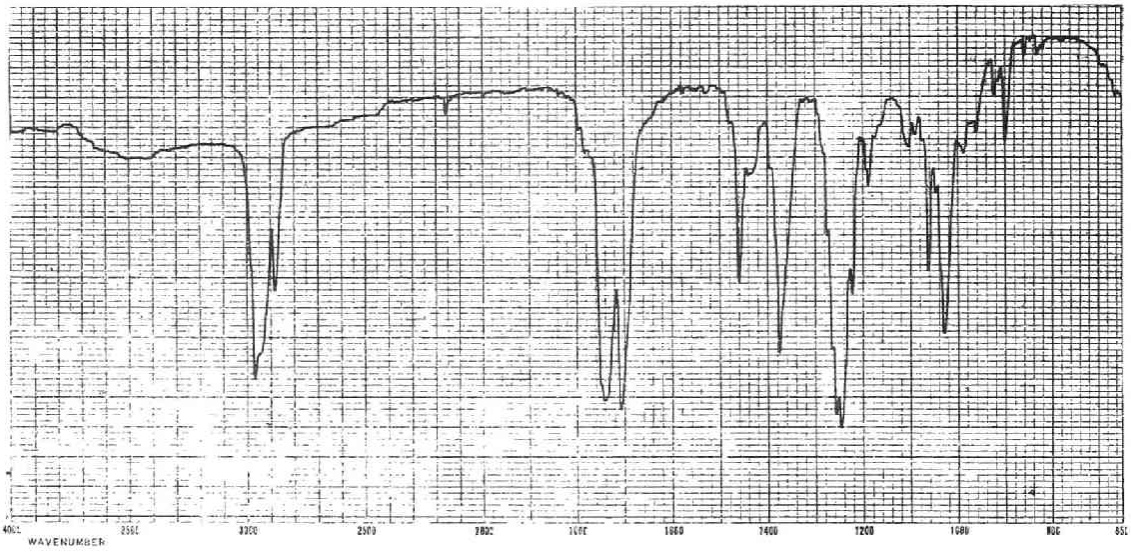
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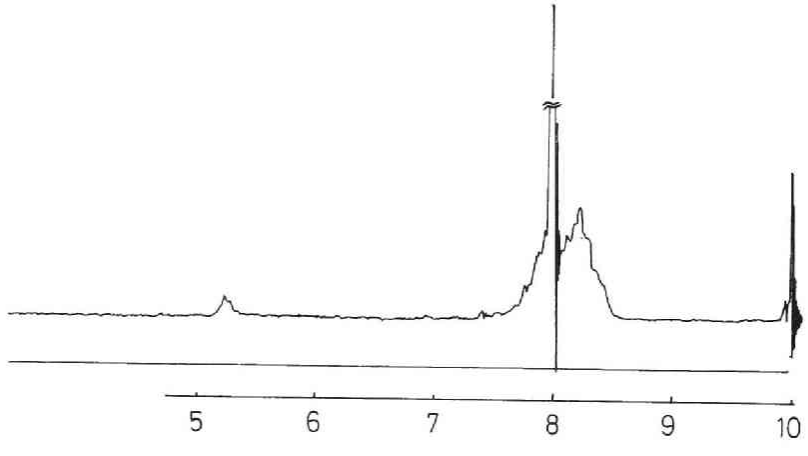
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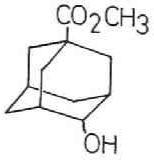
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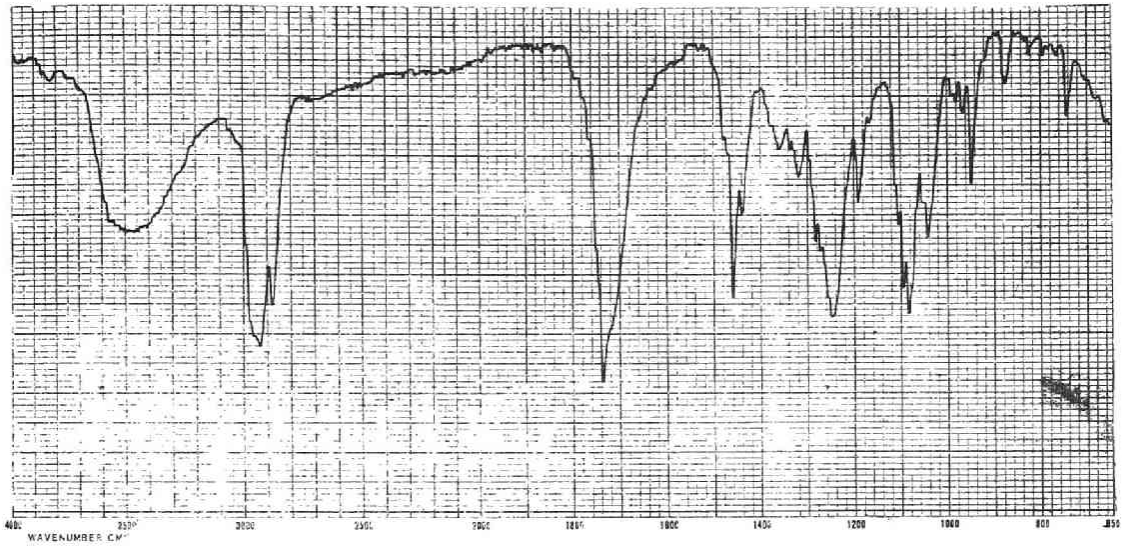
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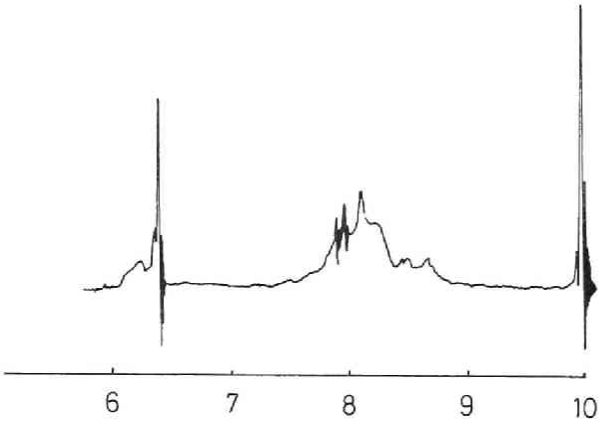
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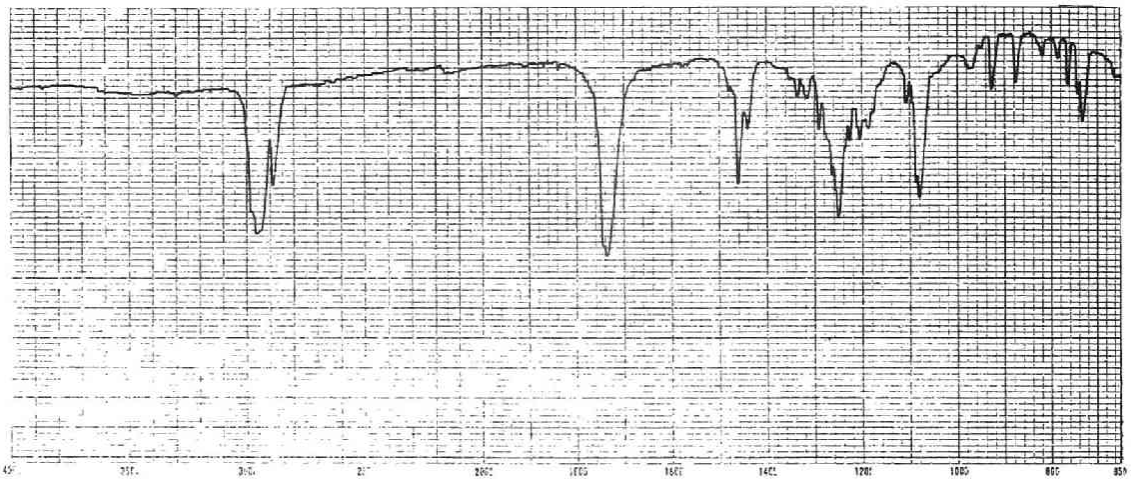

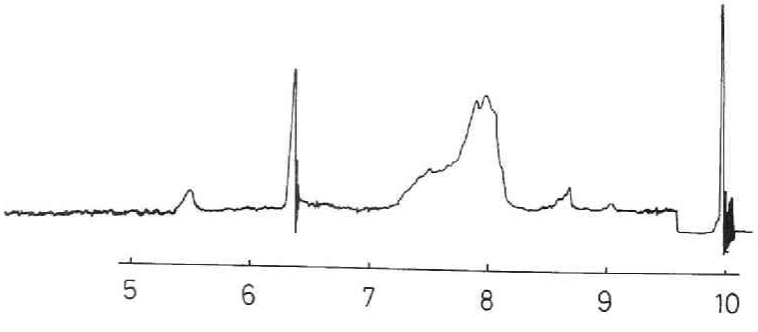
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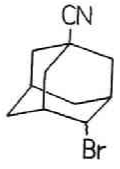
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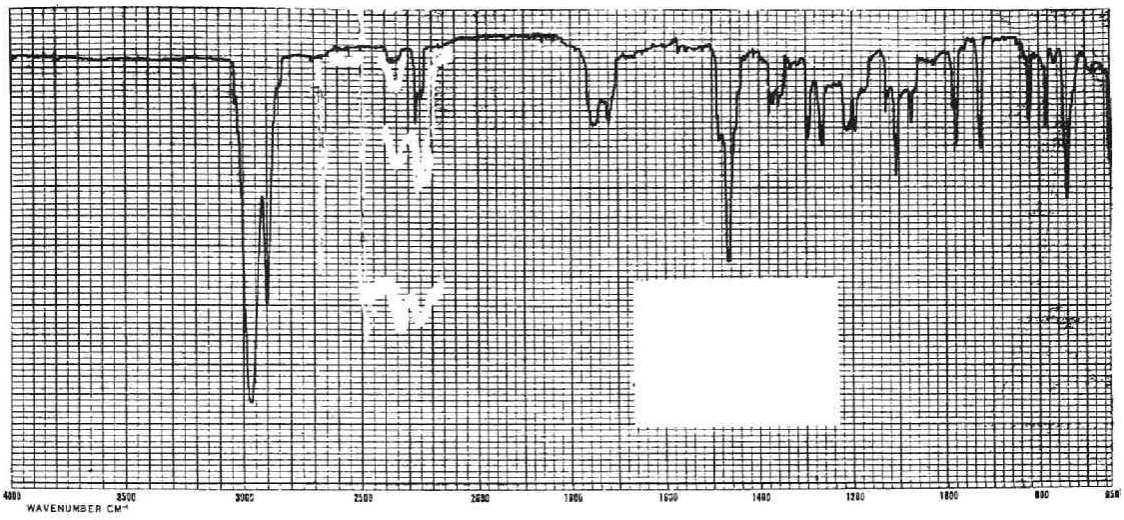
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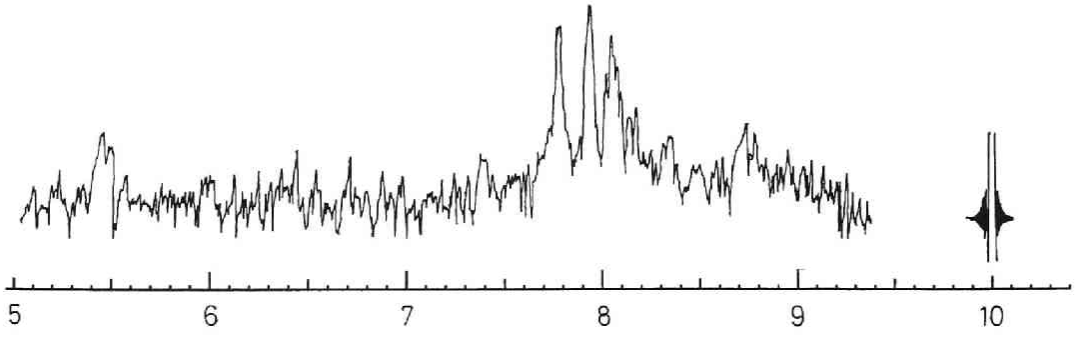
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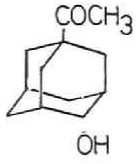
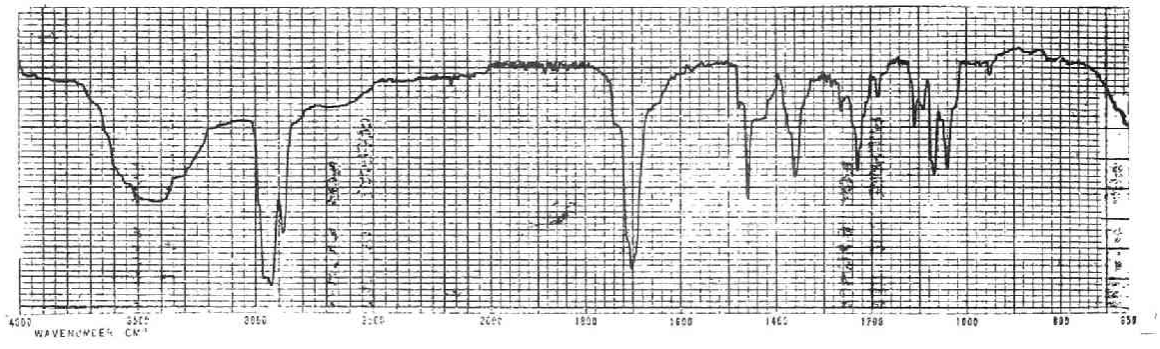
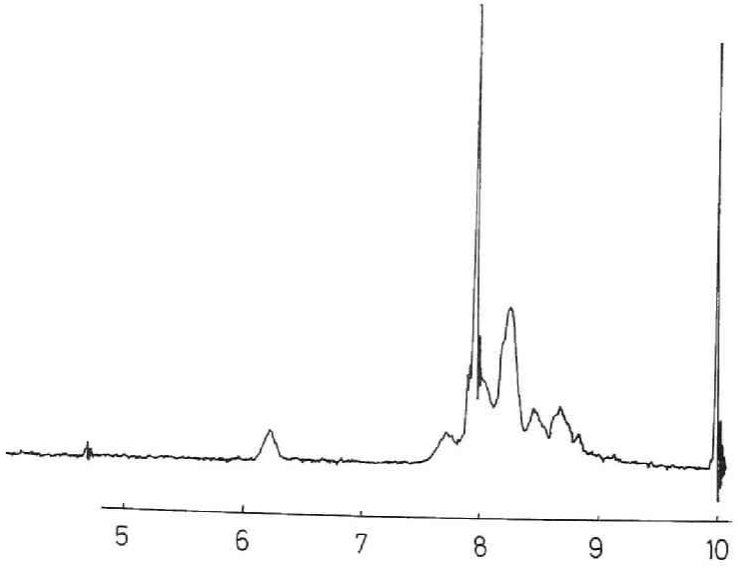
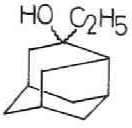
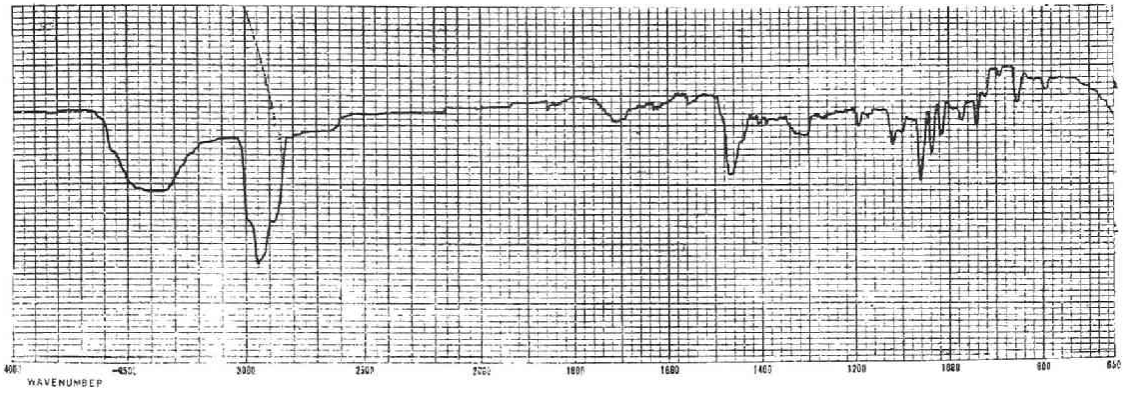
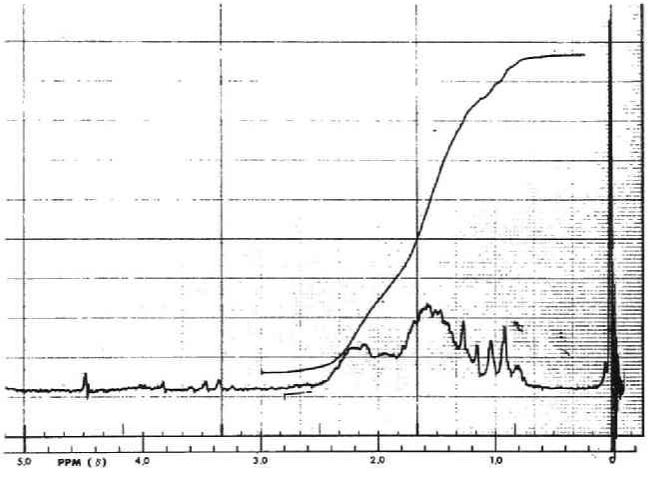

COCH3
OH


4000
WAVENUMBER CM-1

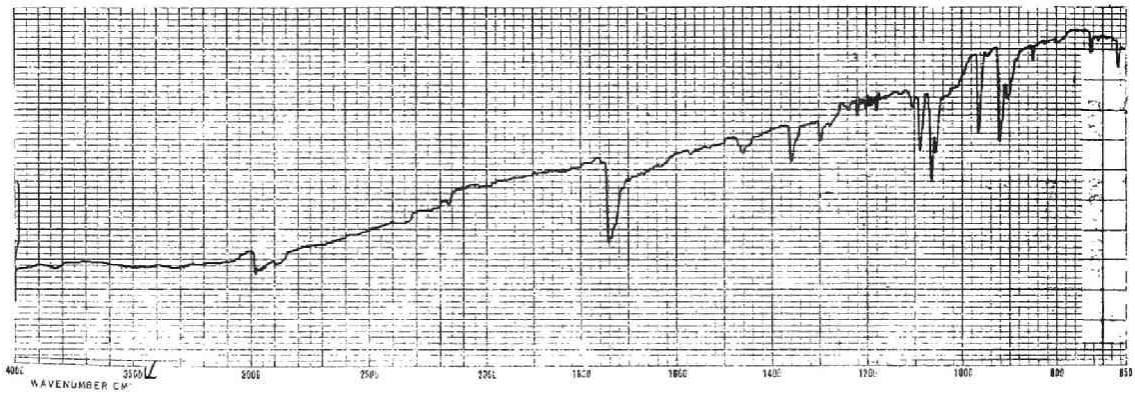

5
6
7
8
9
10

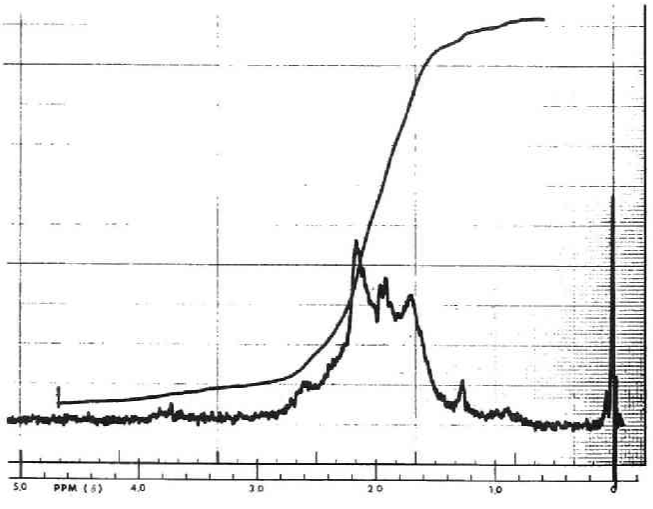

HO
C2H5

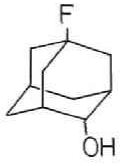

WAVENUMBER
3000
2500
1800
1600
1400
1200
1000
800

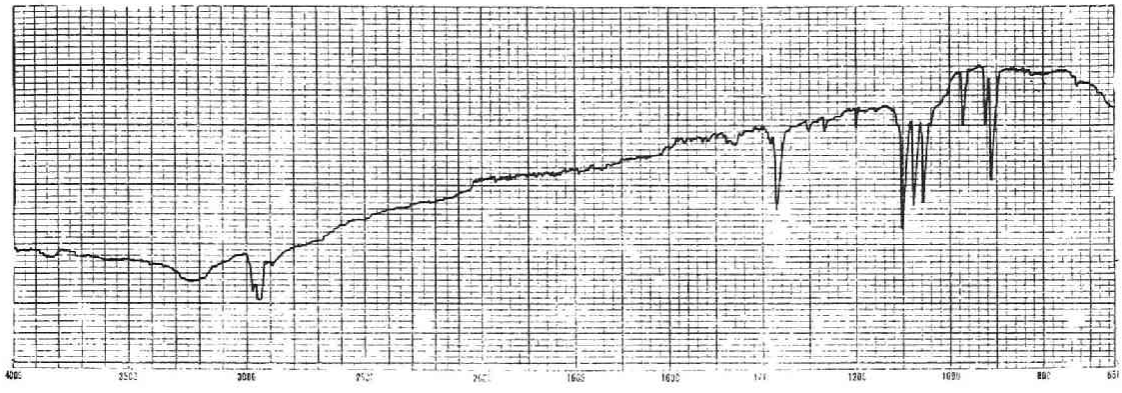

5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

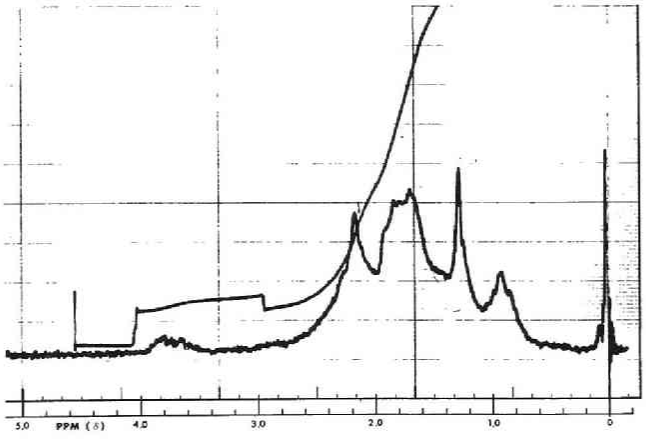

F
O

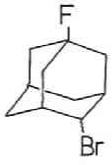

WAVENUMBER CM

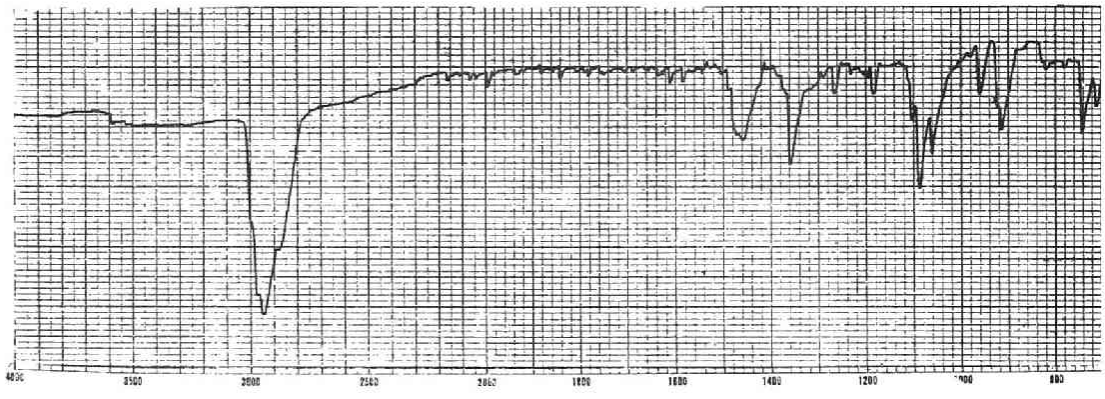

5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

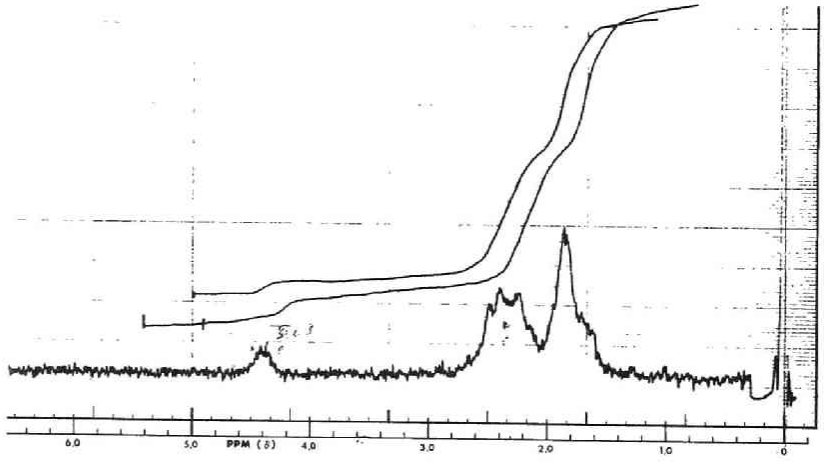

F
OH

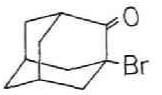


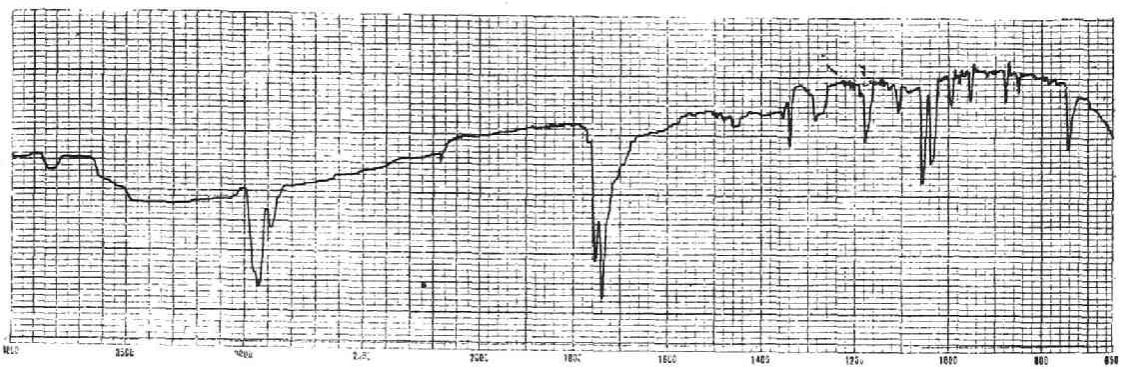

5,0
PPM (δ)
4,0
3,0
2,0
1,0
0

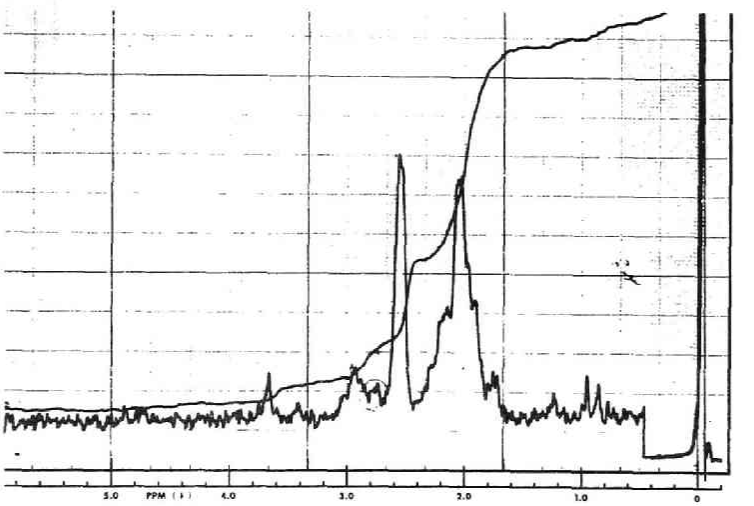

F
Br

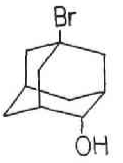


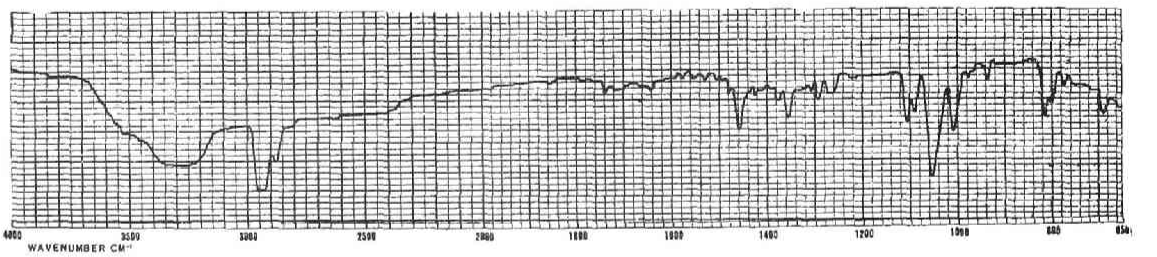

6,0
5,0
PPM (δ)
4,0
3,0
2,0
1,0
0

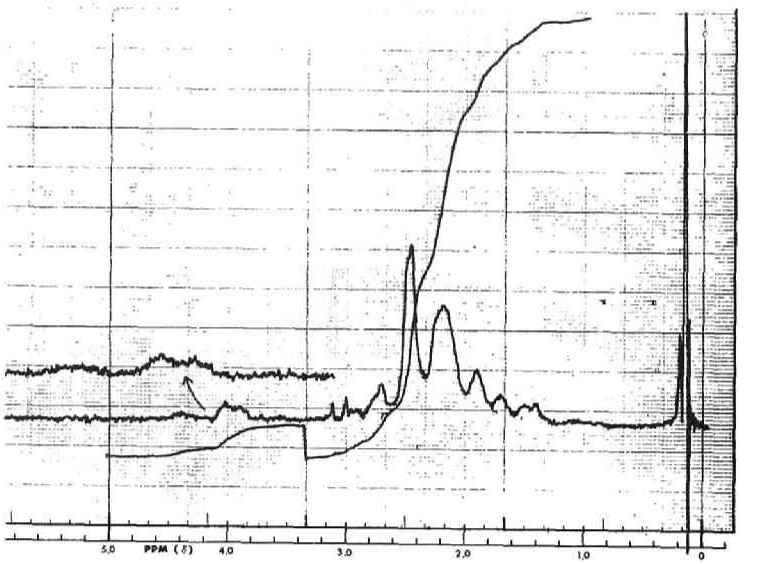

O
Br



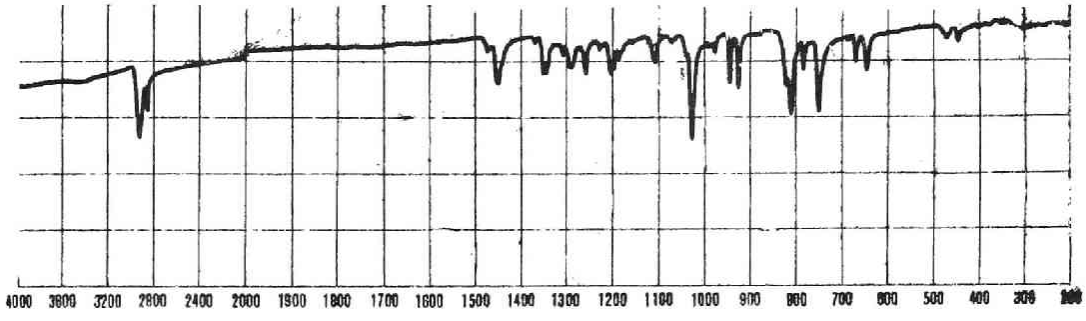

5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

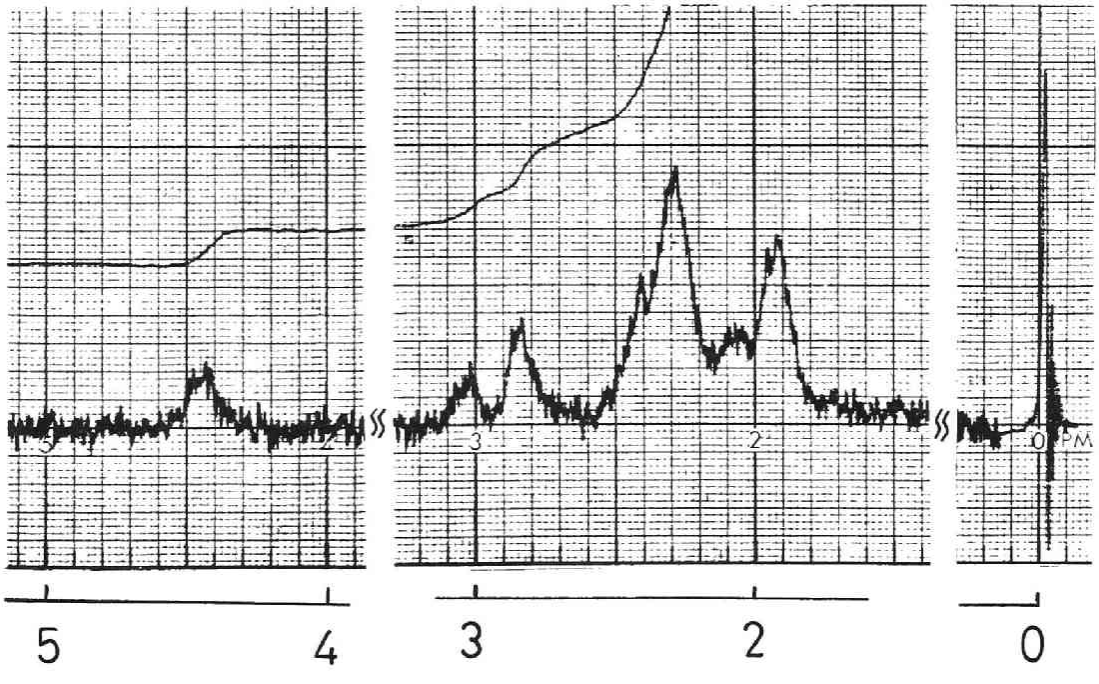

Br
OH


WAVENUMBER CM⁻¹

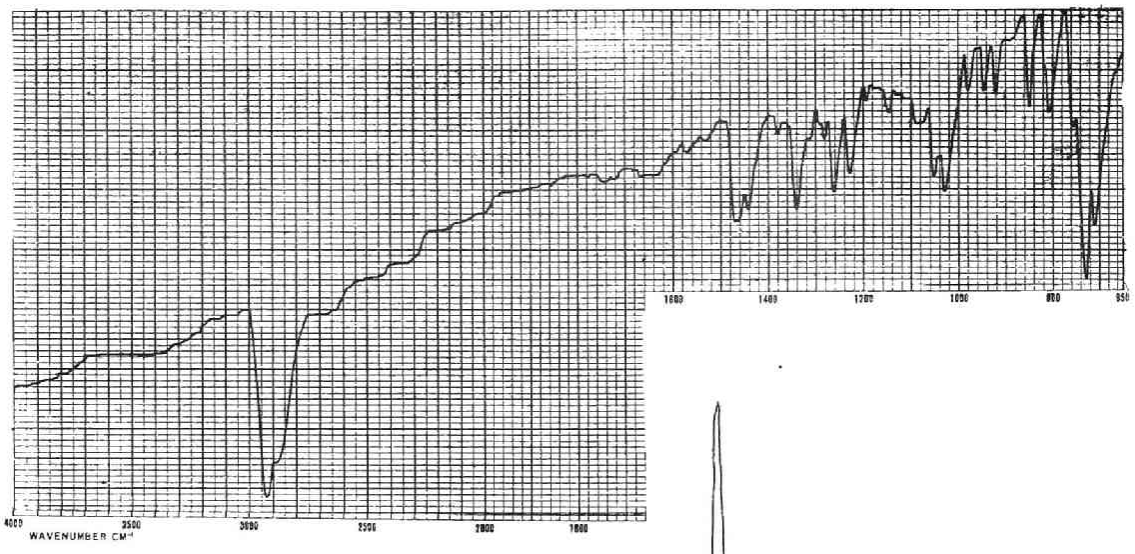

5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

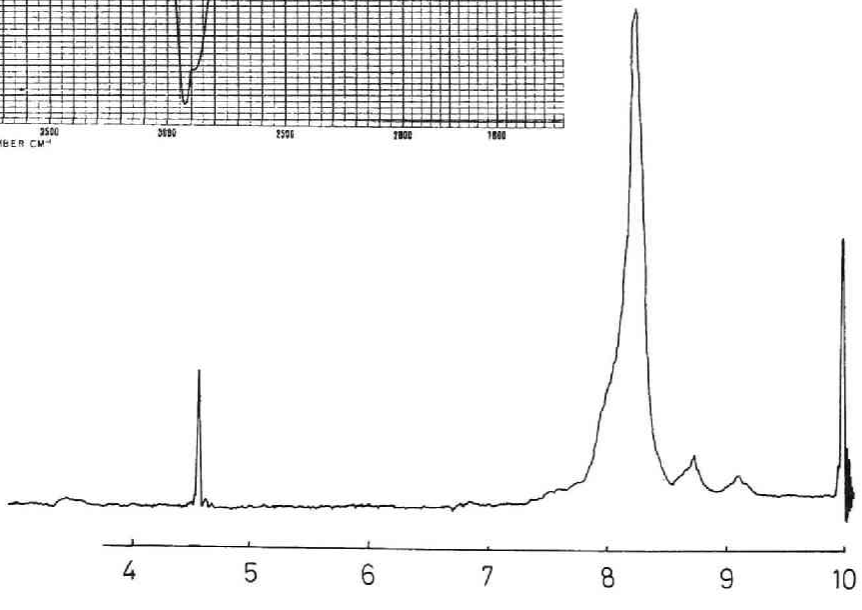

Br
Br

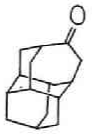

4000 3600 3200 2800 2400 2000 1900 1800 1700 1600 1500 1400 1300 1200 1100 1000 900 800 700 600 500 400 300

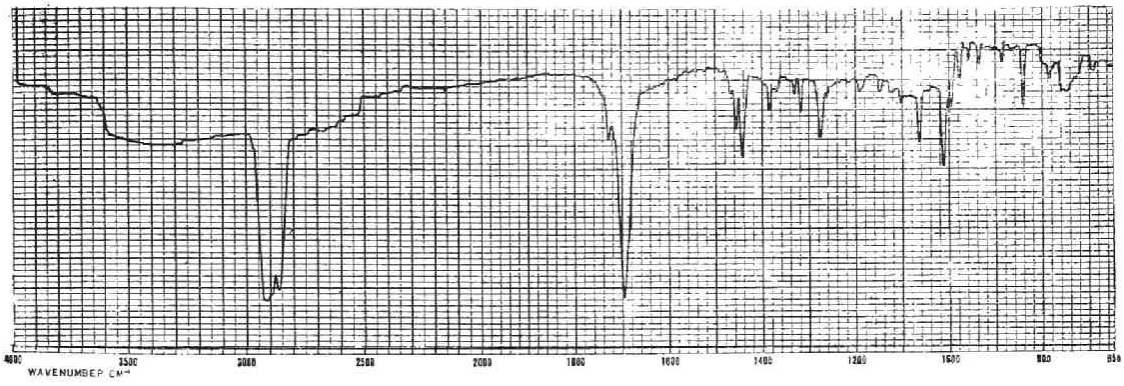

5
4
3
2
0

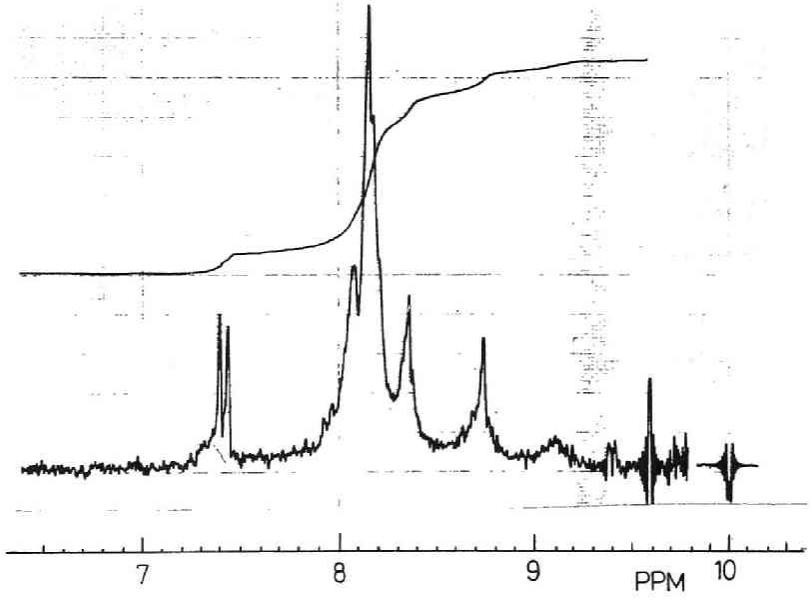

CHCl2

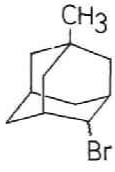

WAVENUMBER CM⁻¹

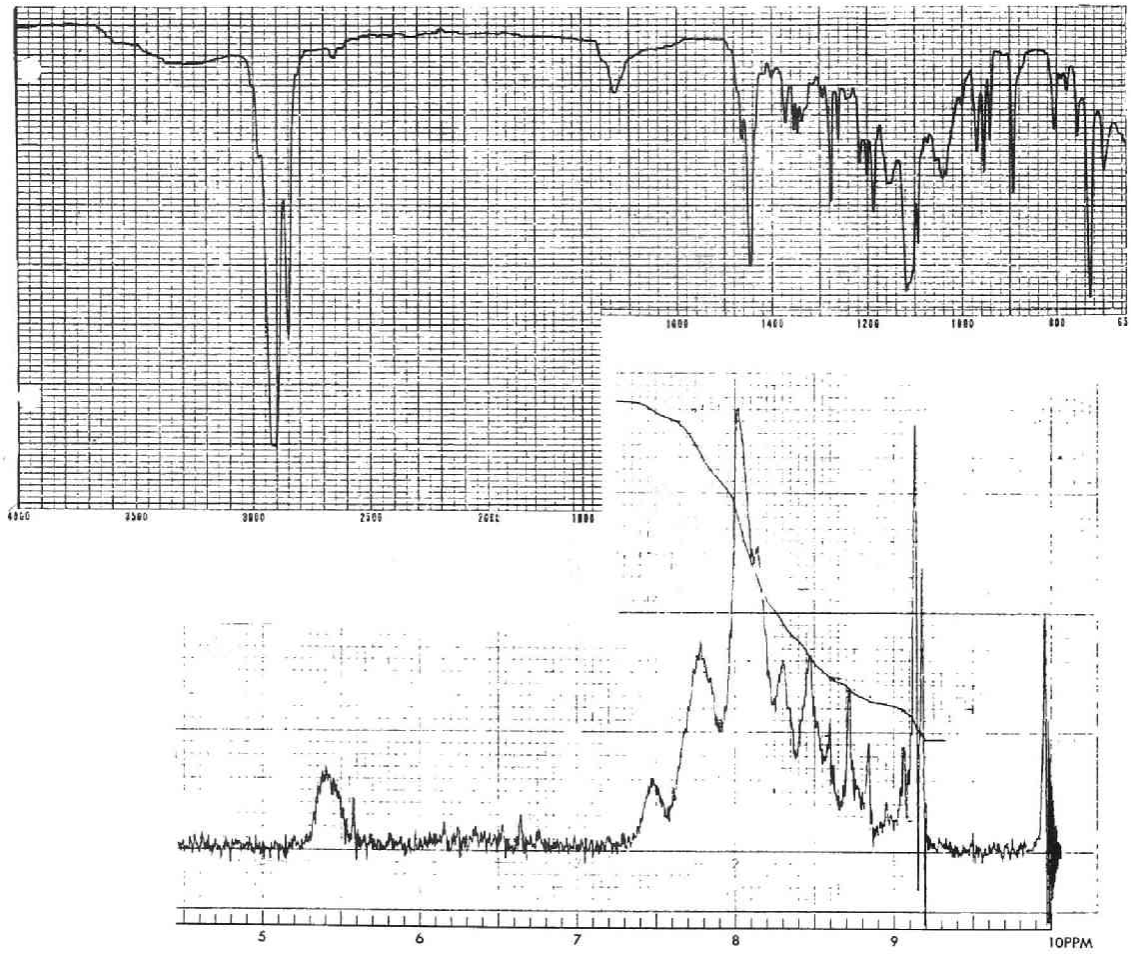

4
5
6
7
8
9
10

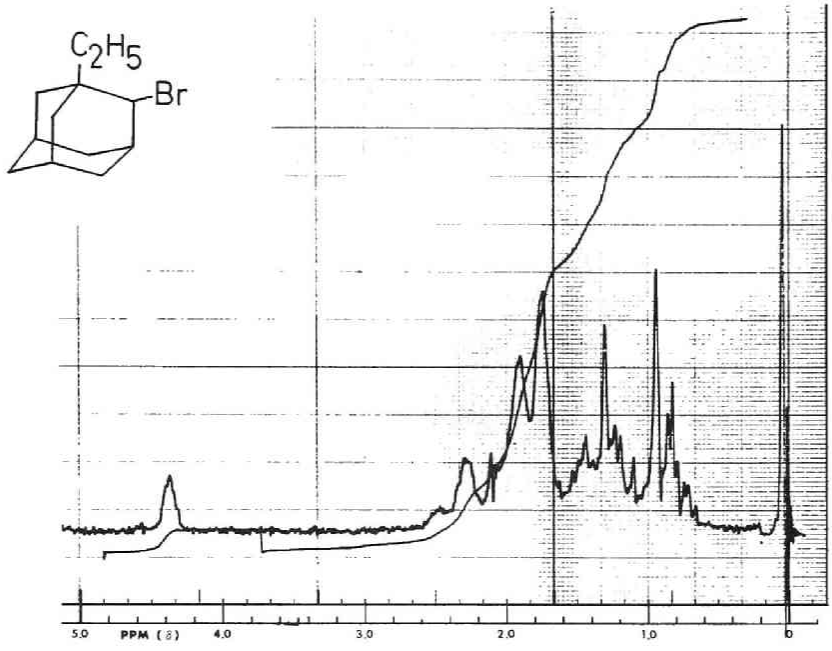


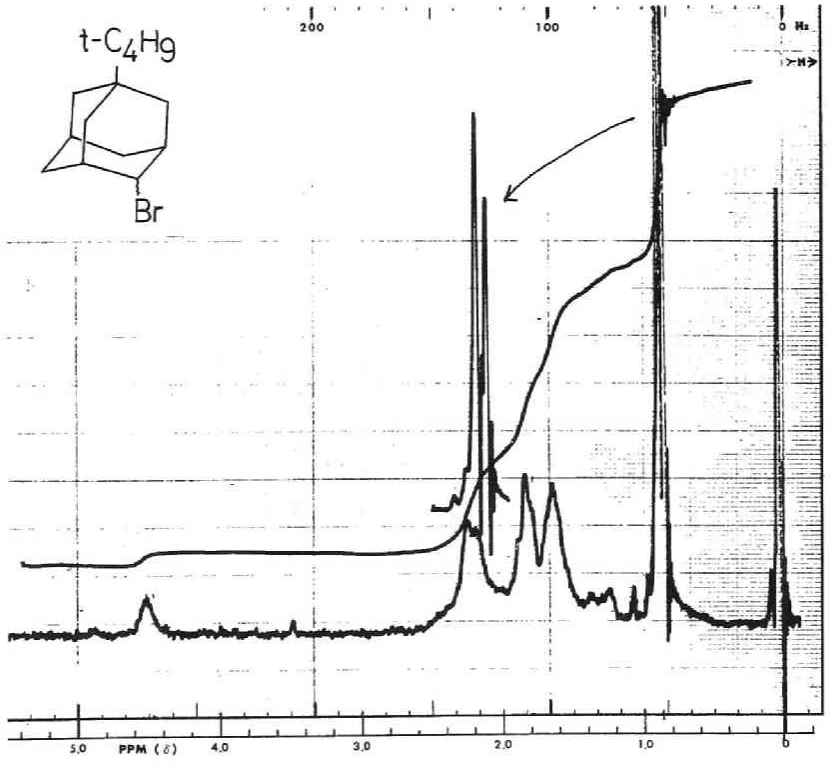

WAVENUMBER CM⁻¹

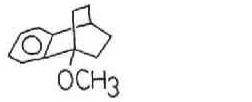

7
8
9
PPM
10

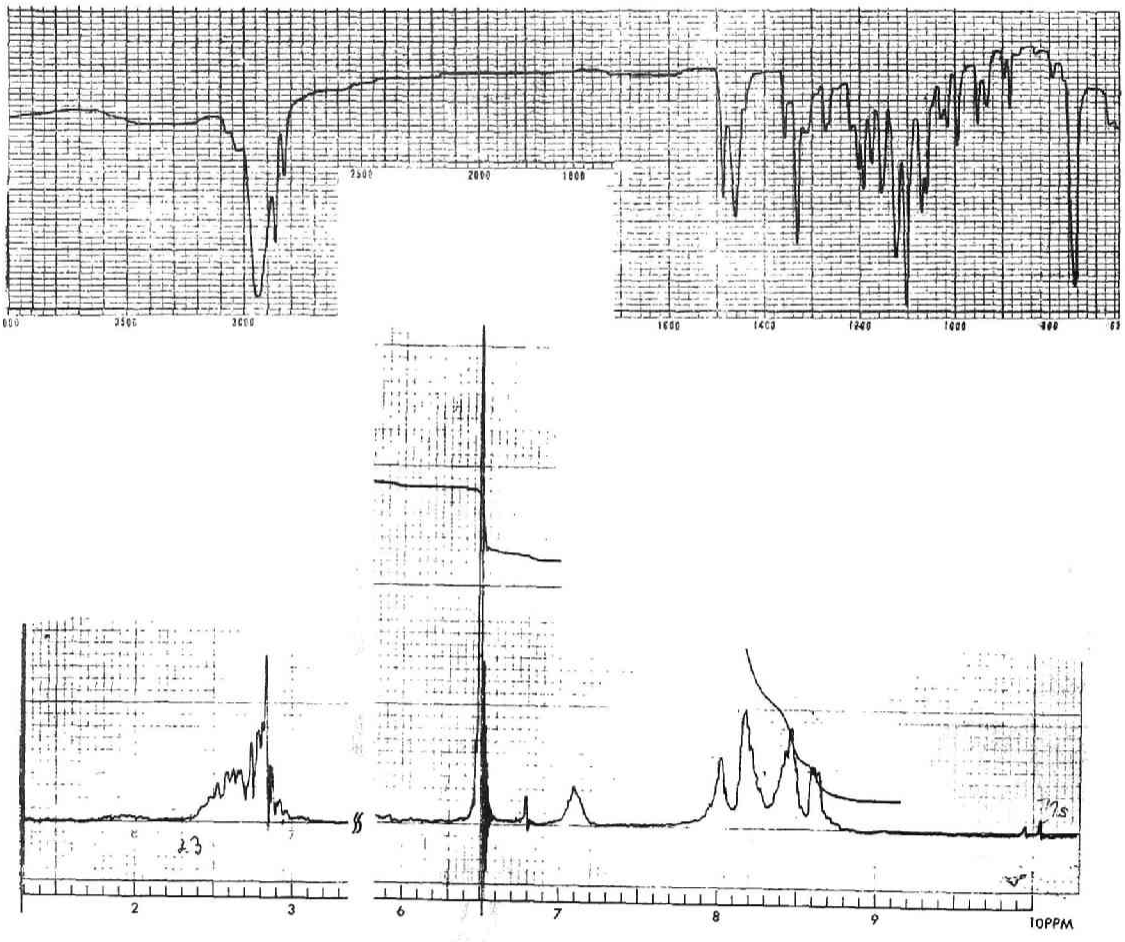

CH3
Br


5
6
7
8
9
10PPM

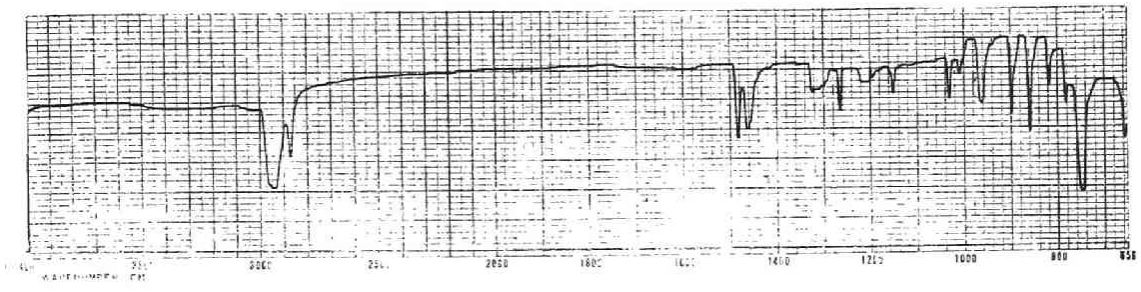

C_2H_5
Br
5,0
PPM (δ)
4,0
3,0
2,0
1,0
0

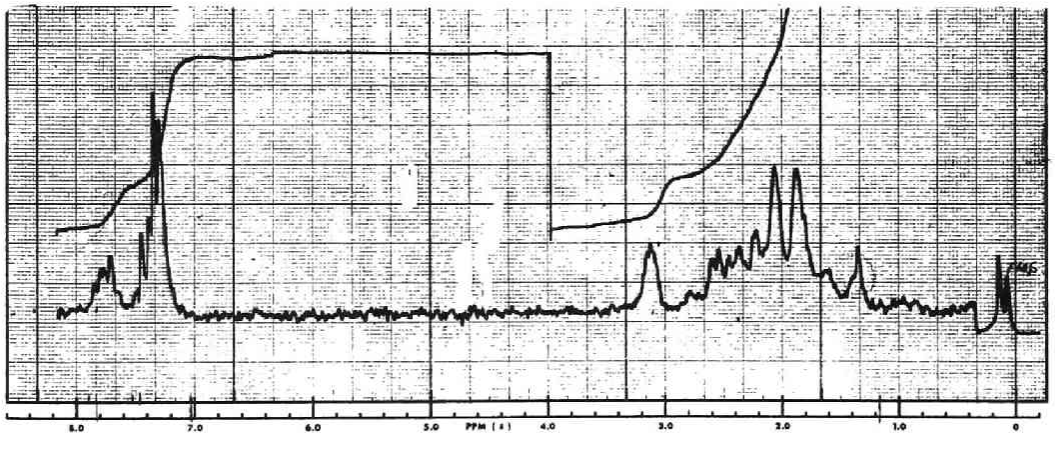

t-C_4H_9
Br
200
100
0 Hz
5,0
PPM (δ)
4,0
3,0
2,0
1,0
0

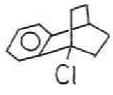

OCH3

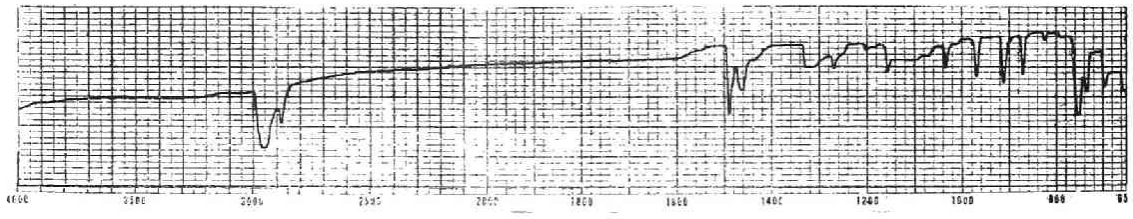

2500
2000
1800
1600
1400
1200
1000
2
3
6
7
8
9
10PPM

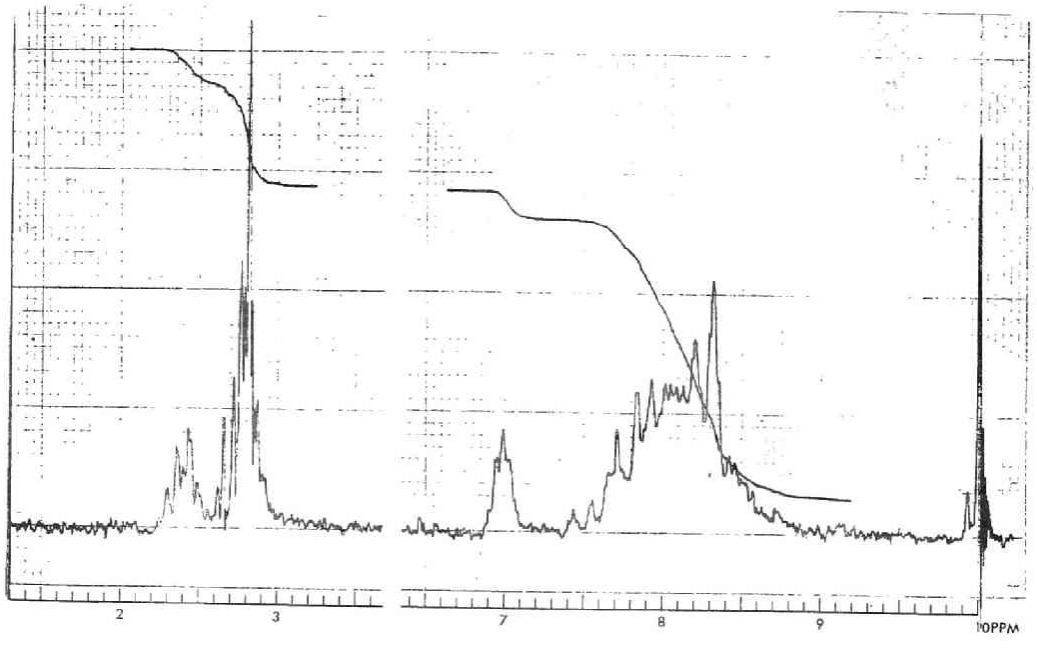

Br


3000
2850
1800
1400
1200
1000
800
650

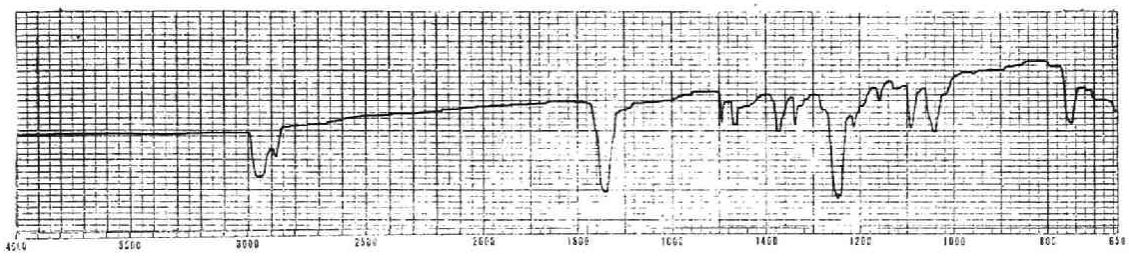

8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

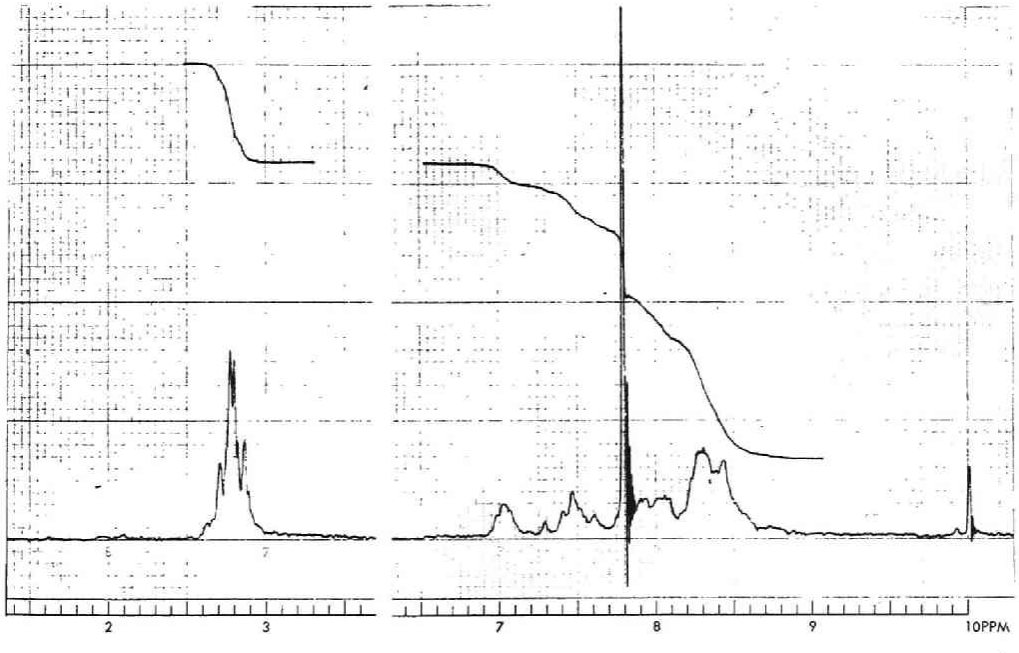

Cl

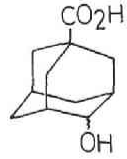


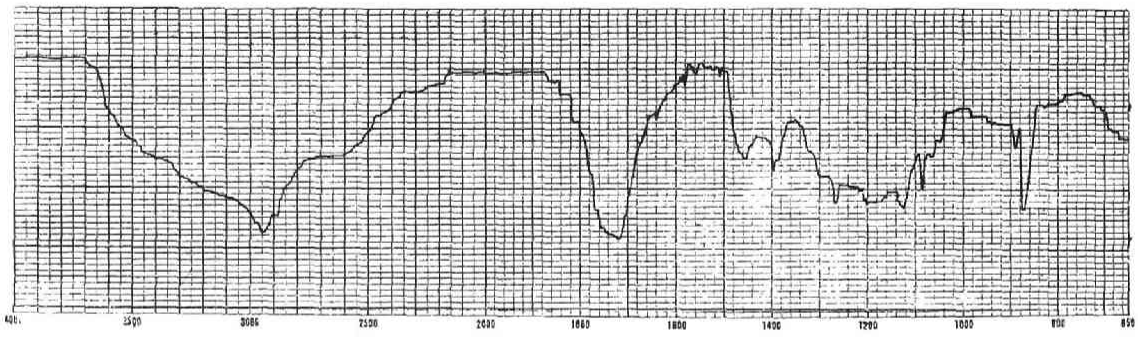

2
3
7
8
9
PPM

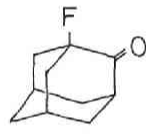

OCOCH3

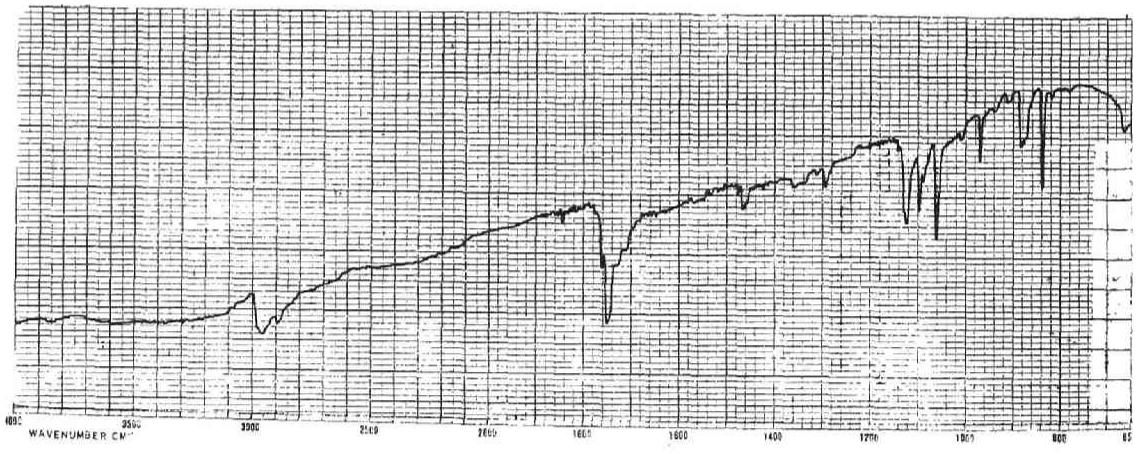



2
3
7
8
9
10PPM


CO2H
OH

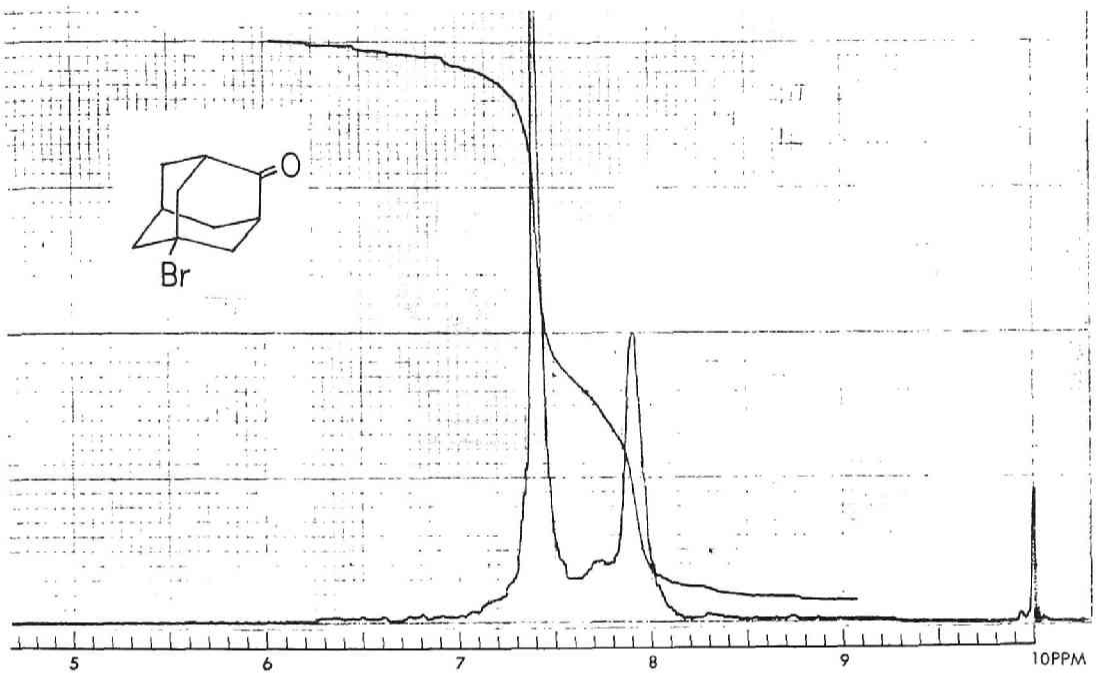


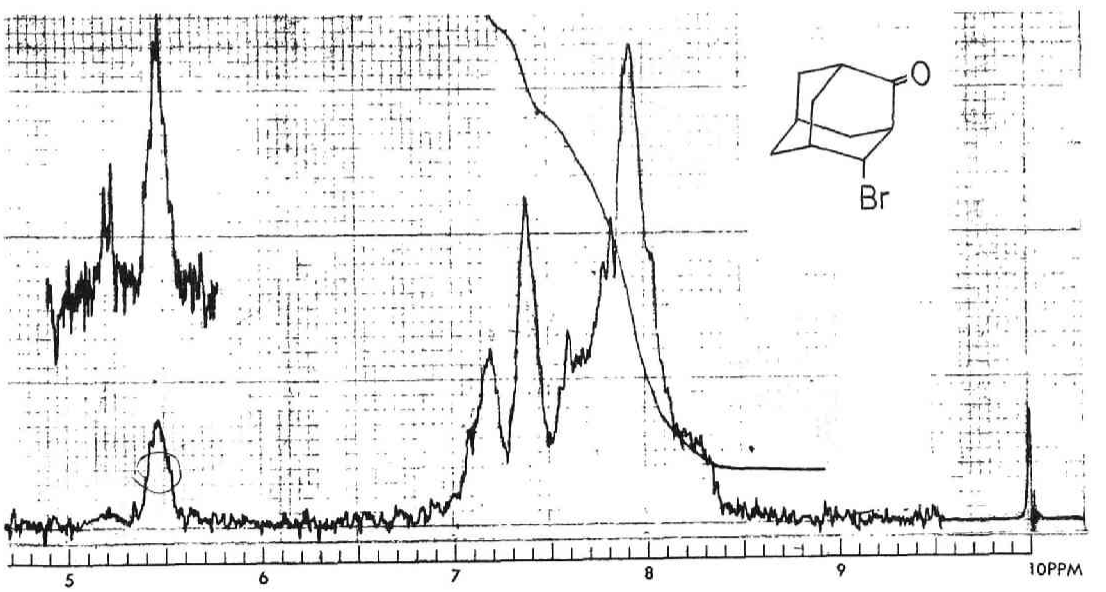

F
O

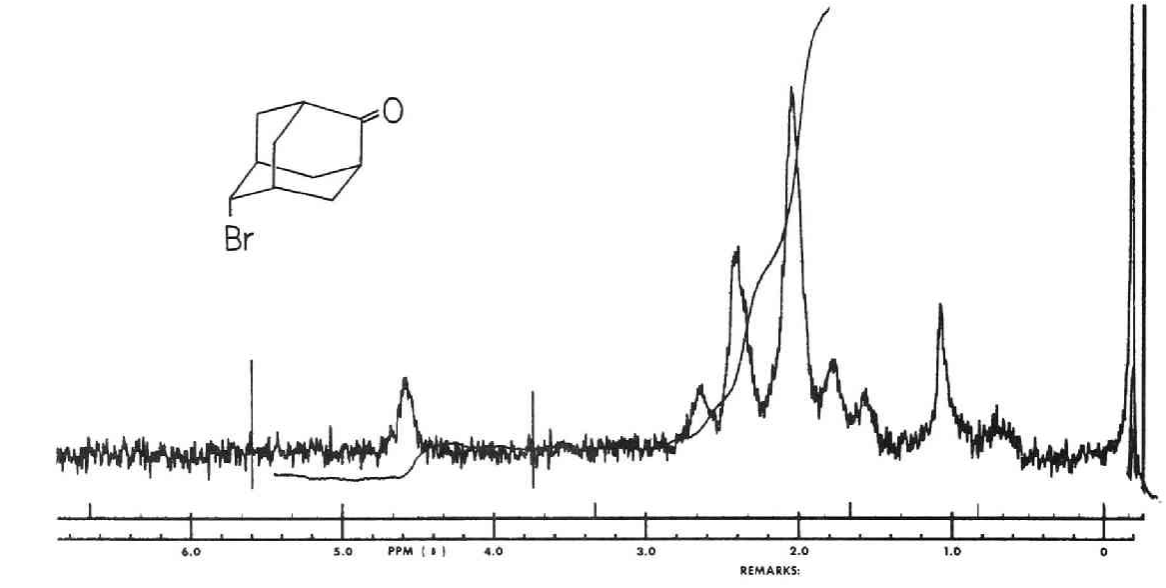

WAVENUMBER CM

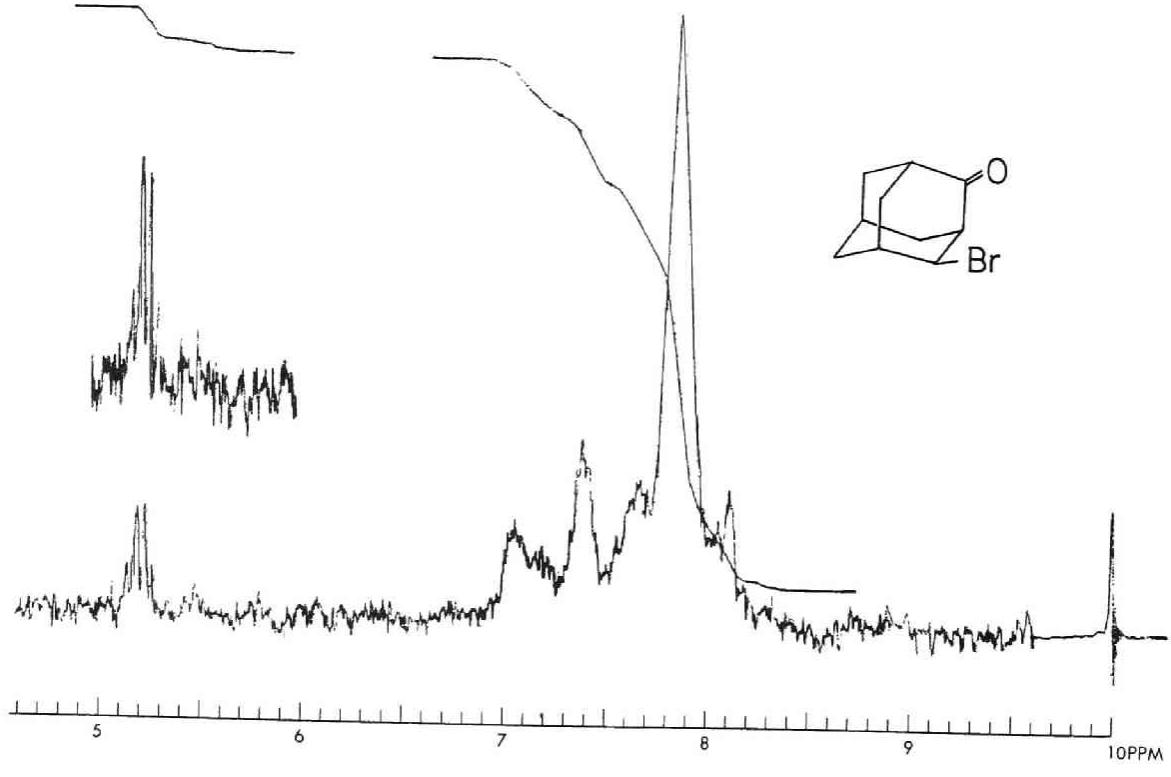
NMR Spectra of Isomeric Monobromoadamantanones

Nmr spectrum of α-bromoadamantanone, see page167



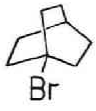


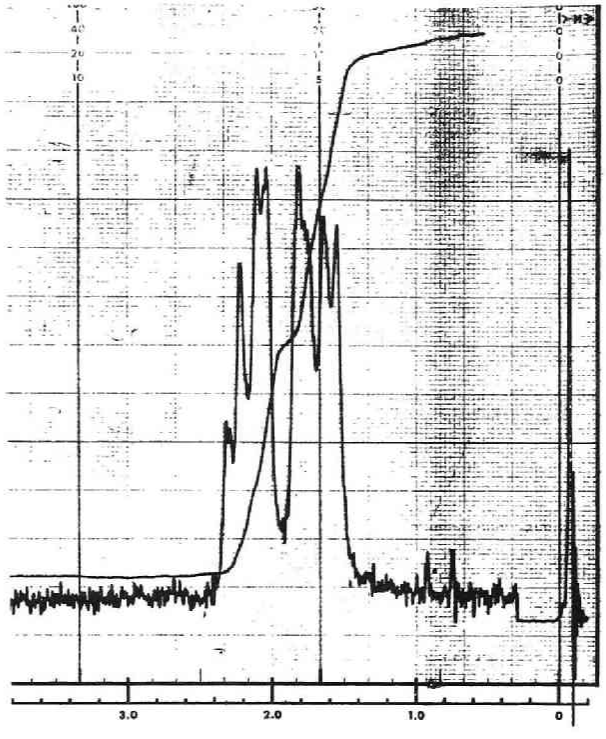

O
Br
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0
REMARKS:

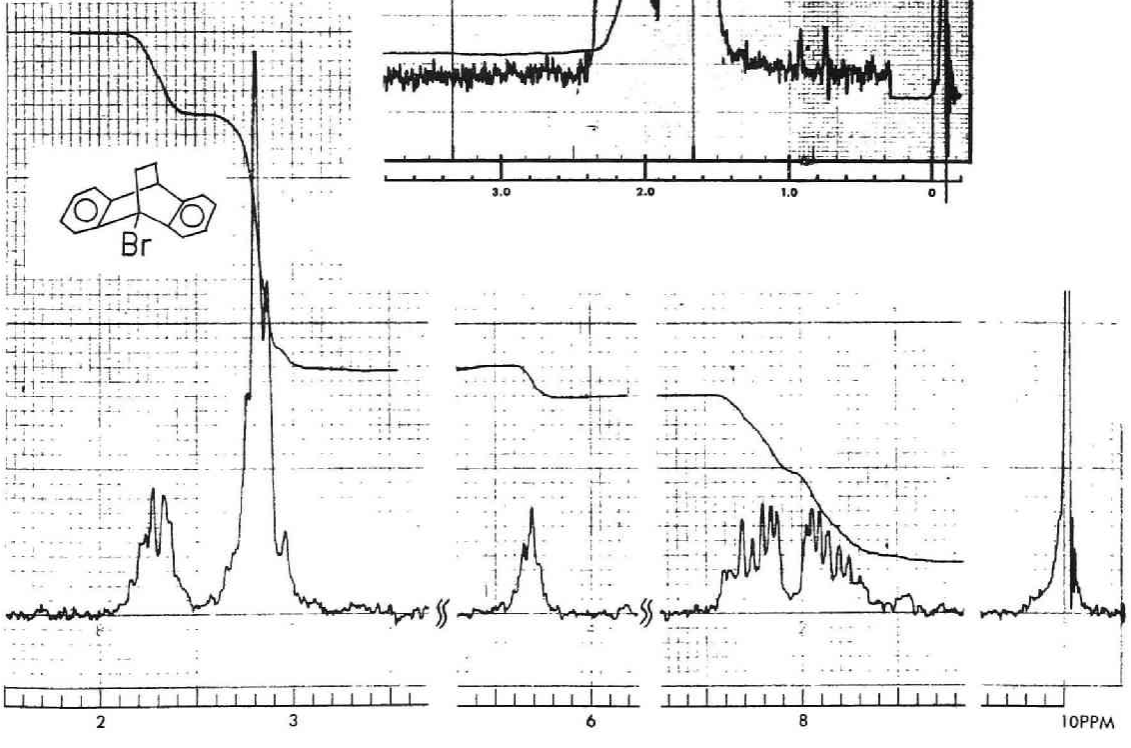

O
Br
5
6
7
8
9
10PPM

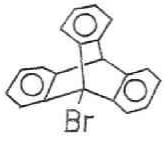
NMR Spectra of 1-Bromopolybenzobicyclo(2.2.2)oct apolyenes

Nmr spectrum of 1-bromobenzobicyclo[2.2.2]octene, see page 175





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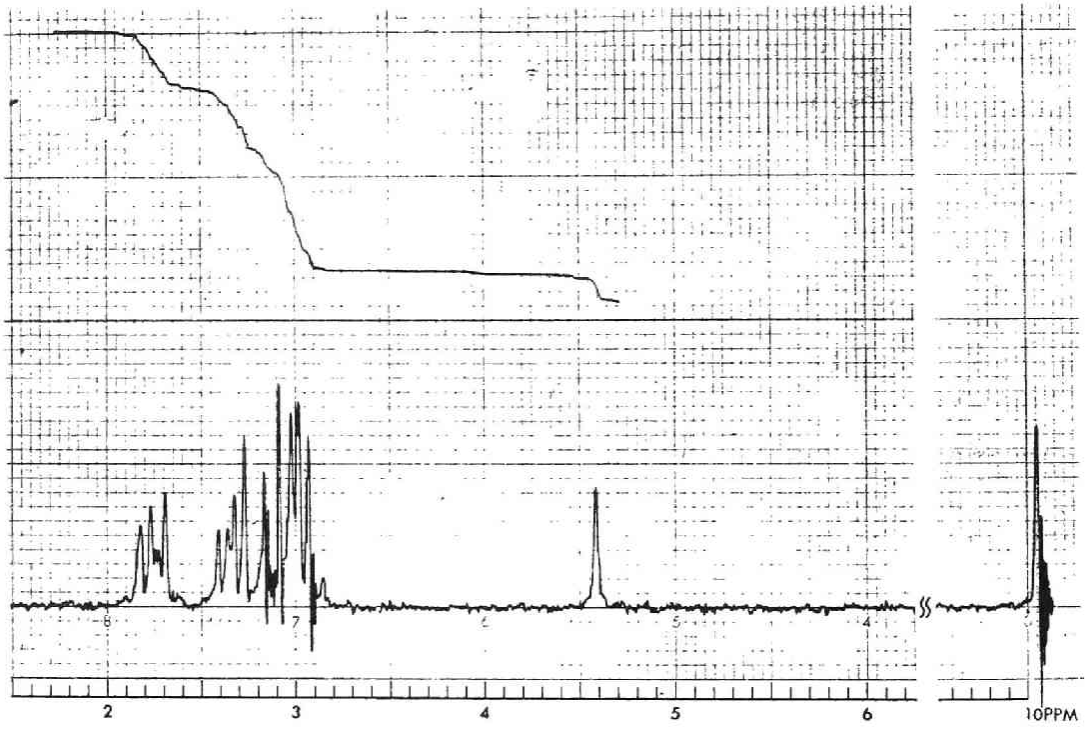
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Publication List

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I. Tabushi and Y. Aoyama, J. Org. Chem., 38, 3447 (1973).

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To be published.

Oral Presentations List

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I. Tabushi, Y. Aoyama, Z. Yoshida, and R. Oda, 23rd Annual Meeting of the Chemical Society of Japan, Tokyo, 1970.

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